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Six More Clinical Trials Proposed For High Priority Status, But Per Case Funds For Them Not Assured

Six additional clinical trials have been proposed for "high priority" status by chairmen of the clinical cooperative groups and the staff of NCI's Div. of Cancer Treatment. Group chairmen approved the selection at their meeting last week; members of the DCT Board of Scientific Counselors, who

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In Brief

Metcalf, Sachs, Nowell, Rowley, Elkind Win 1989 GM Awards; Ray Morrison Retires

WINNERS OF 1989 General Motors Cancer Research Foundation Prizes: **Donald Metcalf**, professor of cancer biology the Walter and Eliza Hall Institute of Medical Research in Victoria, Australia, and **Leo Sachs**, head of the Dept. of Genetics at Weizmann Institute of Science in Israel will share the Sloan Prize for significant basic research advances in clarifying the underlying nature of cancer; **Peter Nowell**, professor of pathology and laboratory medicine at Univ. of Pennsylvania, and **Janet Rowley**, professor of medicine at Univ. of Chicago, will share the Mott Prize for important recent contributions to understanding the causes or prevention of cancer; and **Mortimer Elkind**, chairman of radiology and radiation biology at Colorado State Univ., will receive the Kettering Prize for outstanding recent advances in the diagnosis or treatment of cancer. Each of the three awards is worth $100,000 plus $30,000 for a scientific conference or workshop. . . . **RAY MORRISON**, key NCI staff member in the Cancer Centers Program for the last 12 years, retired June 2 after 15 years with NCI and 33 years in the federal government. He plans to move to the mountain community of Brevard, NC, "where I'm going to take it easy" . . . . **AMONG 40** new members elected to the Institute of Medicine were the following involved in cancer related research: **Thomas Caskey**, director of the Institute for Molecular Genetics, Baylor College of Medicine; **Myron Essex**, professor of virology and chairman of cancer biology, Harvard; **Robert Gallo**, chief of NCI's Laboratory of Tumor Cell Biology; **David Korn**, dean of Stanford Univ. School of Medicine; **David Kuhl**, chief of nuclear medicine at the Univ. of Michigan Medical Center; and **Christopher Walsh**, chairman of biological chemistry and molecular pharmacology at Harvard. Retiring Surgeon General **Everett Koop** was one of five elected directly to senior membership.

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Six Clinical Trials Proposed For High Priority, Maybe With No Money

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heard presentations on the trials at their meeting last week, will be asked to vote on the selections by mail ballot.

The board meeting was held prior to the cooperative group chairmen's meeting. The process established by DCT for selection of high priority trials requires approval by the chairmen before action by the board.

The Cancer Therapy Evaluation Program of DCT initiated the high priority system two years ago as a means of stimulating patient accrual to those clinical trials deemed most important or most urgent to complete. At that time, the cooperative groups were under strong pressure from then NCI Director Vincent DeVita, DCT Director Bruce Chabner and then CTEP Director Robert Wittes to speed up accrual.

The high priority designation is based on the prevalence of the disease, whether the trial represents an important clinical opportunity or an urgent scientific question and the biologic importance of the anticipated findings.

Designation as high priority last year and in the current fiscal year carried with it additional funds for payment by case, which has been considered a key factor in stepping up accrual. Whether the DCT budget will include any money for payment by case in the high priority trials in FY 1990 remains to be seen.

The new high priority trials being proposed are:

<> National Surgical Adjuvant Breast & Bowel Project protocol B18, randomizing patients with operable breast cancer to chemotherapy before surgery (neoadjuvant), or after surgery. The diagnosis is based on needle biopsy. Although most patients will have stage 2 breast cancer, there will be some stage 1 patients since the status of the axillary content is not known until the surgery. Chemotherapy consists of four cycles of adriamycin and cyclophosphamide. All patients over age 50 receive tamoxifen.

<> NSABP protocol B21, to determine the worth of tamoxifen and the worth of breast irradiation in the management of patients with node negative, clinically occult invasive breast cancer. Patients are randomized to one of three arms: tamoxifen alone; breast irradiation and tamoxifen; or breast irradiation and placebo.

<> Southwest Oncology Group protocol 8897, an intergroup study comparing adjuvant chemotherapy with and without endocrine therapy in high risk node negative breast cancer patients; and a natural history follow up study of low risk node negative patients. High risk patients will be randomized either to six cycles of CMF or six cycles of CAF, with each arm further randomized to five years of tamoxifen or no further treatment. The chemotherapy regimen compares the value of adriamycin vs. methotrexate, both in combination with cyclophosphamide and 5-FU.

<> Radiation Therapy Oncology Group phase 3 study in unresectable nonsmall cell lung cancer comparing conventional radiation therapy alone vs. neoadjuvant chemotherapy plus conventional radiation therapy vs. hyperfractionated radiation therapy alone. Chemotherapy consists of vinblastine and cisplatin.

<> Eastern Cooperative Oncology Group/ intergroup protocol for small cell lung cancer randomizing patients to conventional radiation therapy plus VP-16 and cisplatin vs. the same chemotherapy plus hyperfractionated radiation therapy.

<> Intergroup study 0089 for Dukes B_2 (with bowel obstruction or perforation) and C colon cancer, comparing combinations of 5-FU with high and low dose leucovorin and 5-FU with gamma interferon, with surgery only controls. This study is being carried out in two sections. Cancer & Leukemia Group B, ECOG and SWOG randomize patients to observation only after surgery vs. surgery followed by 5-FU and low dose leucovorin vs. surgery, 5-FU and high dose leucovorin. The North Central Cancer Treatment Group and M.D. Anderson Cancer Center randomize to surgery only vs. surgery, 5-FU plus low dose leucovorin vs. surgery, 5-FU and interferon.

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NCCTG Chairman Charles Moertel, in presenting the case for high priority status for the colon cancer trial, acknowledged that earlier studies with 5-FU and levamisole as the adjuvant chemotherapy now in follow up and analysis might soon make it impossible to continue the surgery only arm in the leucovorin trial (**The Cancer Letter**, June 9).

"We want to complete this quickly," Moertel told the group chairmen. "This may be the last colon cancer adjuvant trial with no treatment controls. It is possible it will have to be aborted if interim analysis of the previous trial with levamisole becomes positive. If the (intergroup 5-FU/levamisole trial now with median follow up about three years) is positive, untreated controls will be gone forever."

Moertel said the goal was to accrue 900 patients on the leucovorin and control arms and 300 on the interferon arm. About 270 patients have been entered so far.

Additional funding for the high priority trials remains in doubt. CTEP Director Michael Friedman pointed out to the DCT board that there was $1.4 million in additional money this year for high priority trials. But "we don't know yet if these will have additional funding next year."

"My first priority is clinical trials," Chabner said. "We still have $1.4 million in our budget for next year if we hold the rest of the budget flat. All other grants are getting increases, but cooperative groups are not getting increases."

Moertel's question at the chairmen's meeting about the prospect of additional money for data handling brought the suggestion from Friedman that "we need creative solutions" to the budget problem, with industry as one possible source and help from NCI's other divisions as another.

Industry "could be a tremendous help," Moertel said, although cautioning that priorities of pharmaceutical companies are not necessarily those of NCI or the cooperative groups. "NCI provides a great service to industry (in supporting clinical trials which help in development of marketable drugs). There is a clear obligation on the part of industry." He suggested that CTEP could "broker the deals" between the groups and industry.

SWOG Chairman Charles Coltman suggested that some sort of "entity" could be established to deal with industry "so they can make fiscal contributions to what is going on."

CALGB Chairman Emil Frei mentioned a "small company which wants to interface between cooperative groups and industry." He was referring to Access Biotechnology Inc., headquartered in San Francisco and headed by Michael Goldberg. "Some firms are turned off in working with the groups. They don't see a coordinated approach."

Denman Hammond, chairman of Children's Cancer Study Group, noted that DCT had established guidelines for groups to use in accepting financial assistance from industry. "These mainly involved total disclosure," Hammond said.

"We need to market cooperative groups to industry," Hammond continued. "They don't know much about the groups and would be well advised to learn more. NCI could help, for instance by cross filing on (industry sponsored) agents."

"Industry knows very well about the groups," Moertel said. "Damn near every NDA over the last five years has come out of the groups. Pediatric drugs all come out of your two groups (including the Pediatric Oncology Group, chaired by Teresa Vietti)."

"I'm talking about using the groups for phase 1 and 2 studies," Hammond said.

On extra funding for high priority trials, Moertel said to Friedman, "I'm not optimistic you're going to have much money. Even if you did have more money, some of us might prefer you to require regular peer review to determine the budgets (rather than payment by case).

"Trials to get a cure impact need long term commitments," Moertel continued. "That requires a substantial amount of money. Forty percent of colon cancer accrual is from CCOPs. The CCOP budget comes from the Div. of Cancer Prevention & Control." He commented that CCOPs are not adequately paid for some of the costly trials.

Leslie Ford, chief of the Community Oncology & Rehabilitation Branch in DCPC, responded that CCOPs receive 1.5 credits for patients placed on high priority trials, and 2 credits for some leukemia and pediatric patients.

"But if a trial is not on the board, it only counts for 1 credit even if it is more complicated," Moertel said. "We're scrambling, but we're running a deficit. Accrual to our group had doubled, mostly from the intergroup studies. The deficit is increasing as we accumulate more long term follow up, with

patients living longer. It is really hurting us with no money for data handling."

Hammond observed that designation of high priority trials "has some advantages even they are not backed up with money. The system should not assume there will money for all high priority trials."

Hammond suggested that not all high priority trials had to be intergroup. "If prevalence (of the cancer involved) is an obligate criterion, there never will be a high priority children's cancer trial. Some lesser incidence adult cancer trial could be high priority. Friedman responded that not all criteria listed for high priority are obligates.

Richard Ungerleider, chief of the Clinical Investigations Branch, pointed out that accrual deficit prompted initiation of the high priority system. "In pediatric trials, there has been no problem with accrual."

The high priority system "was an experiment, and I think it has been a qualified success," Friedman said.

That success is measured by a significant increase in accrual during the last two years. Friedman displayed figures for the first quarter of 1989. From Jan. 1 to April 1, the number of phase 3 studies was reduced four percent, with 10 studies closed and four opened. During that time, accrual increased 11 percent over the previous quarter, "a trend the groups should be proud of," Friedman said.

From 1985 to 1988, the cooperative group budget increased from $51 million to $58 million. The number of groups decreased from 18 to 11, and the number of studies open to accrual decreased from 600 to 495.

Despite the small budget increase and decrease in groups and studies, annual accrual increased from 18,200 in 1985 to 21,000 in 1988.

"We're seeing a leaner system, fewer studies but carried out in a more robust way," Friedman said.

"Those are excellent figures," George Lewis, chairman of the Gynecologic Oncology Group, said. He pointed out that many groups are completing many good phase 2 studies which lead to more phase 3 trials. "We'll come back and say that not only are the numbers going up, but more phase 3 studies will exaggerate budget over runs."

Friedman acknowledged the irony. "Here we are, organizing a system which encourages more accrual, higher quality and more sophisticated studies, and then saying we're not going to give you any more money."

At the DCT board meeting, several members had concerns about the high priority trials. James Cox, who is also chairman of RTOG, asked if any of the trials overlapped. "I don't think more than one high priority trial should compete for the same group of patients," he said.

Friedman said that two rectal cancer trials overlap now, and trials have overlapped in the past.

Board members Emil Frei, William Hryniuk and Robert Schimke suggested that more basic science ought to be built into the high priority trials.

Chabner noted that the original purpose of the high priority designation was to provide an incentive to speed up important clinical trials. "If the clinical question itself is not compelling, you shouldn't ask us to put any additional incentive on it," he said.

Board Chairman John Niederhuber said he thought it "unrealistic" to mount a large clinical trial if it had to have a basic science component. Other board members suggested decreasing, rather than increasing accrual, and focusing on basic science.

"That's a total turnaround from what we've been hearing for several years," board member Susan Horwitz said. "We've heard that the clinical trials are so slow that we have to work on increasing accrual."

Chabner suggested that support for basic science research that could be tied in with the high priority trials could come through RO1 and P01 grants.

"The limiting problem is resources," Friedman said. "One of the recurring themes we hear from group chairman is that if they only had more resources, they could provide a lot of science."

DCT Board Approves Recompetition Of Computer Support, Other Concepts

Five major contracts awarded by the Div. of Cancer Treatment involving computer support, compound synthesis, drug storage and distribution will soon be recompeted.

The DCT Board of Scientific Counselors last week gave concept approval for the recompetitions. The largest, a five year contract for a total of $4.3 million, is for the Cancer Therapy Evaluation Program's information system.

All of the concepts were approved unanimously. The texts of the concept statements follow.

CTEP Information system and Drug Management and Authorization Section drug computer system. Recompetition of a five year contract, total estimated award $4.365 million. The current CTEP-IS contractor is Theradex Systems Inc. The DMAS-DCS contract is held by IMS Inc., and a subcontractor, VSE Corp.

This contract supports the computer systems used in CTEP. This consists of two information systems, the CTEP Information System and the Drug Management and Authorization Section Drug Computer System.

CTEP-IS supports the information needs of CTEP by providing comprehensive administrative and scientific information management for each CTEP supported clinical trial from the time it is submitted for review through publication of its results. Reports can be designed in a flexible manner to meet the management needs of various aspects of the program.

DDCS is a database used to verify the accuracy of investigational drug requests and to transmit and record drug shipment information as required by FDA. The system also maintains a listing of NCI approved investigators and updates this listing annually via a reregistration procedure. This entails reviewing each investigator's qualifications and ongoing protocols as required by FDA.

Although the database operates adequately, it does not take advantage of advances in computer technology. To remedy the DDCS's inefficiencies and high mainframe computer costs, the system is being upgraded using existing resources. The design uses a combination of PCs, DCRT and a LAN, which will be located in the DMAS. Enhancement will include a detailed drug usage analysis procedure to control drug supplies. It also will include additional investigator and drug information that will greatly improve the responsiveness of the DMAS staff to investigator inquiries. The proposed upgraded system will be compatible with the CTEP-IS and will continue into this next contract award.

The existing CTEP-IS database will be maintained and further developed, including the establishment of a local area network for the CTEP Protocol Information Office. CTEP wide direct access to the database via the LAN and integration with other databases within CTEP are planned for the future.

The DDCS will continue its initial efforts of conversion to PC. Both the current and the new system will run in parallel for a time to prevent any down time or loss of data.

Synthesis of radiosensitizing agents. Recompetition of a three year award now held by Stanford Research Institute International. Total estimated award $1.842 million.

The least expensive and most promising method of overcoming the resistance of hypoxic tumor cells to radiation has been the use of radiosensitizing agents in conjunction with radiation therapy. This contract complements NCI's radiosensitizer screening contract by optimizing the leads that result from screening. The optimal compound of each new lead, the chemical class that shows radiosensitizing activity, will be tested as it progresses toward clinical trials.

Three important compounds have been developed under this contract: SR-2508, the optimal compound of the nitroimidazole series currently in clinical trial; SR-R233, a specific hypoxic cell cytotoxic agent; and BSO, originally tested as a radiosensitizer and now introduced to the clinic as a chemosensitizer.

Using the principles and approaches learned from the systematic study of the nitroimidazoles and the non-nitro compounds investigated so far, future efforts will be directed toward the optimization of other classes of chemical compounds which show activity in the radiosensitizer screen. Emphasis will be placed on the rational design and development of compounds without the nitro group, which have different mechanisms of radiosensitizing action.

Synthesis of compounds for preclinical toxicology and phase 1 clinical studies. Recompetition of awards held by Aldrich Chemical Co. and Starks Associates. Five year award, estimated annual amount $583,000.

The chemical preparation laboratories are used to obtain data for the preparation of the necessary quantities of clinically important chemicals and to develop the most economical means for their preparation. The conversion of small scale to large scale production often requires developmental studies which are carried out by the contractors. The compounds prepared are not readily available in the quality or quantities needed from the supplier.

The preparation laboratories provide the means of obtaining nearly any type of chemical compound in large quantities. The materials are of very high purity and are well characterized. The quantity of a given material synthesized may range from 50 grams to multikilograms. Compounds received from the contractors are prepared under current Good Manufacturing Practices and are intended for formulation development, toxicology, pharmacology and clinical use in phase 1 trials.

The contracts will be recompeted at a slightly higher level than the current package. Presently, the package represents about six staff years total effort. An increase to a level of eight staff years total effort is necessary to accommodate the new compounds expected shortly from the new in vitro screen. The contractors are currently operating at full capacity with the compounds currently in development for toxicology and phase 1 clinical trials.

Preparation of bulk chemicals and drugs for phase 2 and 3 clinical trials. Recompetition of contracts held by Aldrich Chemical Co., Starks Associates, Ash Stevens Inc., Pharm-Eco Laboratories Inc. Estimated annual amount $1.5 million, five year award.

(See description in previous concept statement).

This contract will be recompeted at a slightly higher level than the current package. The package presently represents about 14 staff years total effort. An increase to 16 staff years is necessary to accommodate the higher work load which has resulted from increased patient accrual on clinical trials.

Storage and distribution of clinical drugs. Recompetition of a contract held by ERCI Facilities Service Corp. Estimated annual amount $550,000, two years.

This contract provides for the receipt and storage of chemical and biological products for investigational chemotherapy. These clinical products are stored under specified conditions, inventoried and shipped to authorized investigators in the U.S. and other countries for clinical trials under investigational new drug applications. This contract supports all of the intramural and extramural DCT clinical trials research efforts by supplying the final dosage forms to be tested in cancer patients. For patients undergoing IND chemotherapy, the timely delivery and receipt of drugs can be life saving.

In addition, this contract maintains a computerized data processing and analysis system to manage and maintain the drug inventory and repository functions. The contract also meets all applicable FDA current Good Manufacturing Practices regulations and possesses and EPA Toxic Waste Generator permit and the necessary state and local permits.

The clinical drug storage and distribution operation has received, stored, shipped and maintained records on hundreds of dosage forms and has made more than 100,000 shipments since 1986. The contractor currently processes more than 65 shipments a day, an increase of 45 percent since 1986. All drug shipments are packaged in conformance with the applicable regulations for shipping drugs and the appropriate supplies, materials and procedures for each type of order. The contract has been responsive to the program's needs by making personnel available on numerous occasions at night and on weekends for emergency shipments.

During the past year, the contract implemented a new automated inventory control system, the Pharmaceutical Data System, designed to meet the growing needs of PRB. This system currently works in parallel with the DDIS, the system it is to eventually replace.

The RFP will be issued during fiscal year 1990. This contract will involve the use of contract facilities and capabilities to provide a resource for the storage and distribution of the clinical drugs for DCT. The work scope will involve the receiving of all clinical drug items, proper storage of these items, the packaging and distribution of them to authorized clinical investigators, and the creation and maintenance of

adequate computerized records of all transactions so adequate inventory records and operating levels of NCI drug supplies can be maintained and monitored. In addition, the capability to arrange for special packaging and labeling of drug products, and the blinding of drugs and their distribution for double blind studies will be available.

To accommodate growing demands, additional room temperature and refrigerated storage space need to be obtained, about 5,000 additional square feet. The 198 percent increase in ice shipments is a direct result of the continued growth in biological response modifiers. The special packaging and thousands of pounds of dry/wet ice needed to ship these pharmaceuticals have increased shipping costs dramatically. Additional personnel, shelving, and refrigerator space all need to be incorporated into the estimated funding and space allocation of this contract. Adequate records will be maintained to meet all of the requirements of NCI, FDA, DEA and EPA. These records will include receiving and distribution, quarantine, expiration, sampling required and a variety of routine and special activity reports.

Board member Robert Schimke asked whether the three drug synthesis, storage and distribution contracts could be combined into one large contract. Michael Boyd, director of the Developmental Therapeutics Program, said this was done once, but it proved "incredibly complicated."

Schimke said he had once requested methotrexate for laboratory testing, but NCI said the drug was being used for clinical trials. "Obviously, there is some competition for these compounds," he said. He pressed Boyd on which request would have priority, the clinical request or the laboratory request.

Boyd said it would have to depend on the circumstances. "I think you are better off using a drug first to find out its mechanism of action," Schimke said.

"We try to, but sometimes you have to push ahead on trials," Boyd said.

DCT Director Bruce Chabner said he would note the concern about providing drugs for preclinical studies. "We're talking about only $20 worth of drugs," he said.

FDA Advisors Recommend Approval Of Leucovorin, Hexamethylmelamine

The FDA Oncologic Drugs Advisory Committee has recommended approval of hexamethylmelamine for second line therapy of stage 3 and 4 ovarian cancer after patients have failed previous chemotherapy, and of leucovorin in combination with 5-FU for metastatic colorectal cancer.

The committee recommended against approval of hexamethylmelamine as first line therapy of stages 3 and 4 ovarian cancer as part of the H-CAP regimen (including cyclophosphamide, adriamycin and cisplatin).

The committee's recommendations on hexamethylmelamine (Hexalen is the trade name, owned by U.S. Biosciences Inc.) represented a solid consensus. The vote for second line therapy was unanimous except for two abstentions, and the vote against first line therapy was opposed only by Teresa Vietti. FDA staff also appeared to favor those recommendations, which indicates probable approval by the agency.

The recommendation for leucovorin, however, came on a 5-4 split vote, with some committee members arguing the data were too premature to determine whether leucovorin combined with 5-FU showed a significant survival benefit over 5-FU alone to outweigh the greater toxicity.

Lederle Laboratories submitted the supplemental new drug application for leucovorin, which is already approved as an antidote to high dose methotrexate.

Lederle proposed that prescribing information for leucovorin include the treatment of locally advanced or metastatic colorectal cancer, at a dose of 200 milligrams per meter squared intravenously, followed by 5-FU at 370 mg/m^2 intravenously, daily for five days. The results of four controlled trials were presented to support the application.

Three of the four studies showed response rates between 26 and 44 percent for patients who received leucovorin, compared to 7 to 10 percent for patients receiving 5-FU alone. In the fourth study, patients on the leucovorin arm had a response rate of 19 percent, but their duration of response was 100 days longer than the control group's duration.

Time to progression ranged from one and a half to four months, and median survival was about a year for the patients on leucovorin.

Toxicity included mucositis, diarrhea, nausea and vomiting, and leukopenia.

Robert DeLap, of Lederle, noted that since most patients entered in colorectal cancer studies eventually die of the disease, improvements in time to progression "may be an excellent surrogate endpoint for survival in colorectal studies."

Part of the reason some committee members may have decided against approval was that some of the data presented were interim results that had not been submitted with the application.

Michael O'Connell, of the Mayo Clinic, presented interim results of the North Central Cancer Treatment Group's study of additional patients accrued after the NDA was submitted. Those data show objective response rates of 33 percent each for the two treatment arms that received leucovorin, compared to 7 percent of the control group, which received 5-FU alone.

David Hersey, executive secretary of the committee, said the committee does not have to consider data that it had not seen before its meeting.

The Mayo Clinic has discontinued 5-FU alone and uses leucovorin in combination with 5-FU as its standard for advanced colon cancer, O'Connell said.

The North Central study also found that low dose leucovorin was more effective than high dose leucovorin, because the dose of 5-FU could be increased. In that arm, 44 percent of the patients responded. O'Connell said that in subsequent studies, Mayo Clinic is using the low dose formulation, which is 20 mg of leucovorin, followed by 425 mg of 5-FU, daily for five days. An advantage to that dosage is the lower cost, he said.

Lederle sought approval for high dose leucovorin. Several committee members said there was not enough information to make a recommendation on the dosage.

Robert White, who presented FDA's comments on the application, said the data were unclear on the efficacy of leucovorin.

"The modest prolongation of survival by weeks or months is overshadowed by toxicity," White said. "5-FU plus leucovorin did not significantly increase survival in any study in which patients had measurable disease."

Committee member Robert Capizzi, who was the primary reviewer for the committee, said White's analysis did not include O'Connell's additional data. He asked the committee to recommend approval of leucovorin.

While the new indication will not be a "breakthrough," Capizzi said, three of the four studies did show significant improvements. More work should be done to lessen the toxicity and increase response rates, he said.

Committee member Albert Bernath said he agreed. "I don't consider that there is any effective therapy for colon cancer." He said the data on leucovorin has been shown to be reproducible, had high response rates, including some complete responses. He noted that the toxicities were manageable, and the studies had very low patient dropout rates indicating that patients did not feel too sick to continue treatment.

Committee members voting against the NDA were David Ahmann, Sandra Horning, Chairman Robert Bast, and Thomas Fleming. Those in favor were Capizzi, Bernath, Teresa Vietti, Grace Monaco, and Craig Henderson.

Philip Schein, president of U.S. Bioscience, presented the case for hexalen. The studies supporting the new drug application were carried out before the two year old firm obtained the rights to the agent.

Hexalen was first found active against ovarian cancer 25 years ago at Vanderbilt, Schein said. The 41 percent response rate was as good as that of adriamycin, platinum and alkylating agents, he claimed.

A phase 2 Eastern Cooperative Oncology Group study using hexalen with cyclophosphamide, adriamycin and platinum (CHAD) had a median survival time of 23.5 months. A phase 3 ECOG study in 253 patients reported a median survival time of 19.6 months.

Schein also referred to a Mt. Sinai study and to an unpublished ECOG study to support the NDA. In the unpublished study, patients had greater tumor bulk, with one fourth of them having tumors 10 cm or greater. Median survival was 46 months for those on the H-CAP regimen, compared to 22 months for CAP alone.

In the Vanderbilt study, patients with limited residual disease had median survival of 107 months with the H-CAP regimen compared to 20.7 months with CAP, Schein said.

"These studies demonstrate that hexamethylmelamine increases survival, some to an unprecedented extent, especially with tumors smaller than 3 cm," Schein said.

John Johnson, FDA medical officer, questioned the validity of historical controls used in most of the studies. He pointed out that 19 of 73 patients in the Mt. Sinai study were excluded from the evaluation. He cited other studies in which little difference was noted in survival between patients receiving regimens with hexalen or not.

Ahmann, primary reviewer for the committee, said the unrandomized trials troubled him. "I'm not convinced hexamethylmelamine has an advantage."

"It is difficult to evaluate, particularly for first line therapy," Horning said. "Results of the Vanderbilt study, with minimal disease, are impressive. I'm concerned about the lack of supportive studies."

Fleming said that "an over all comparison seems to show hexamethylmelamine does not increase responses. In a log rank comparison, there is a definite lack of any benefit." He added that a Mayo Clinic study found an increase in peripheral neurotoxicity. "We had difficulty keeping physicians accruing because of this toxicity."

Bast said he was encouraged "even if there is only a handful" of long term survivors. "The number of patients who respond to second line therapy are so few. It should be available in the community. We should approve it as second line therapy and encourage research in combinations for first line."

The drug has been available as an NCI Group C drug. Approval of the NDA would remove it from that list.

FDA, NCI In Spirit Of Cooperation, Seek Compromise On Endpoint

There are signs that a new spirit of cooperation has descended over the once fractious relationship between NCI and the Food & Drug Administration. Although there is still disagreement over the use of survival as an endpoint for the marketing approval of drugs, both sides in the debate appear to be seeking a compromise.

After a relatively cordial and low key meeting between NCI and FDA representatives last week, participants came away more optimistic than before that the two agencies could iron out their differences.

"There's a new spirit of trying to anticipate problems before they arise," said Carl Peck, director of FDA's Center for Drug Evaluation and Research.

Peck met with the Div. of Cancer Treat-Treatment Board of Scientific Counselors last week. The Board had submitted a "white paper" listing its concerns about drug approval to FDA last year, and FDA responded in February.

Since then, NCI and FDA staffs have met four times. "There have been no injuries," Peck quipped. One positive outcome was the early release of levamisole as a group C drug. Another was the idea of a joint NCI/FDA fellowship program in oncology and regulatory science.

This would be a three year program to produce board certified oncologists who have extensive experience in clinical investigation, drug development and regulation, Peck said. The first year would be spent at NCI, and the second and third years would be shared between the NCI's Cancer Therapy Evaluation Program and FDA's oncology section. The first fellows would enter the program in mid-1990.

"We were all impressed with the progress toward resolving our differences," board Chairman John. Niederhuber wrote in a letter to Peck released at the meeting.

The board still is concerned that, "we are both skirting the major issue, that of the regular use of survival as the ultimate endpoint," he wrote. "There are times in oncology when a simultaneous control group to demonstrate survival differences is medically unacceptable."

DCT Director Bruce Chabner agreed. "The problem is most apparent in considering drugs for treatment of cancers for which existing therapies provide some benefits in terms of responses and survival," he said, citing breast cancer, ovarian cancer, lymphomas and leukemias. "For these diseases, NCI would like to see efficacy defined in terms of reproducible response rates, with acceptable toxicity in phase 2 studies."

FDA "continues to ask for demonstrations of equivalence in survival rates in phase 3," Chabner said. "These approval strategies add years to the premarketing phase of drug testing."

While FDA Commissioner Frank Young has advocated approval of drugs for cancer and AIDS after phase 2 trials, FDA staff members define phase 2 as extensive clinical testing, Chabner said. "NCI's definition of phase 2 is a trial that establishes the activity of the drug as a single agent."

Peck said FDA's definition of phase 2 is a controlled, randomized clinical trial. The difference in the two definitions has caused some confusion among clinical investigations and others involved in clinical trials.

Board members said some understanding probably could be reached. Niederhuber and others suggested that some mechanism be set up by which drugs that show efficacy can be tested on a wider basis by qualified investigators. "It seems to me there ought to be a way to reach a middle ground," he said.

Peck said he thought the issue "is clearly resolvable," and that both sides could hold discussions on "what is phase 2."

Robert Bast, chairman of the FDA Oncologic Drugs Advisory Committee, presented five recommendations he said could "improve communication between FDA, NCI and the private sector."

--NCI and FDA should sponsor consensus conferences to identify surrogates for efficacy on a disease by disease basis and publish the results.

--Drugs should be judged by standards clearly established in writing up front at the time of the initiation of trials, rather than at their completion.

--To assure adequate accrual up front when trials are initiated, contact with CTEP should be made. The drug sponsor should work with CTEP to identify adequate accrual of patients in a short period of time.

--There should be an NCI representative on the Oncologic Drugs Advisory Committee.

--NCI should sponsor additional research on quality of life issues, particularly the methodology for assessing quality of life.