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Cancer Groups Support Senate FDA Bill; Reform Measure Faces Uncertain Future

In Senate hearings last week, several advocacy groups representing cancer patients, researchers and care providers expressed support for an FDA reform bill introduced by Sen. Nancy Kassebaum (R-KS).

While several of the groups said they did not support all aspects of the bill, all appeared to be united in the hope that the Senate measure, which is more moderate than the proposals currently emerging in the House,

(Continued to page 2)

In Brief

NIDDK Begins BPH Trial; Roswell Park Honors Schwarzkopf; NRC Cites MIT

LARGEST STUDY to test whether the drugs finasteride and doxazosin can stop noncancerous prostate growth has begun recruitment of 3,000 men at 17 centers, the National Institute of Diabetes & Digestive & Kidney Diseases announced this week. The Medical Therapy of Benign Prostatic Hyperplasia Trial is chaired by **John McConnell**, a urologist at University of Texas Southwestern Medical Center in Dallas. . . . **NORMAN SCHWARZKOPF**, the retired US Army general who was diagnosed with prostate cancer in 1994, received the Gilda Radner Courage Award from Roswell Park Cancer Institute last month. The award recognizes individuals whose diagnosis of cancer has heightened public awareness and inspired courage in other patients. . . . **ERICH LOEWY** was named chair of bioethics, University of California Davis Medical Center. Loewy was a professor at University of Illinois College of Medicine. The chair, underwritten by the medical school's alumni, is one of only a few endowed bioethics chairs in the country. . . . **ANDREW VON ESCHENBACH**, chairman of the Department of Urology, M.D. Anderson Cancer Center, was named to the board of trustees for Catholic Health Initiatives, a new healthcare system encompassing 63 hospitals in 21 states. He also was recently selected to receive the Medical Award of Excellence from Cancer Counseling, a Houston non-profit association. . . . **NUCLEAR REGULATORY** Commission has cited the Massachusetts Institute of Technology for a violation of NRC requirements, the commission said earlier this week. No fine was proposed. MIT was cited for failing to secure radioactive materials following the ingestion of phosphorus 32 by a researcher last August. . . . **CITY OF HOPE** National Medical Center's cancer program has been granted three-year approval by the Comission on Cancer of the American College of Surgeons.

Senate Bill Sets Deadlines For FDA Drug Approvals

(Continued from page 1)
would form the basis of whatever changes would take place at FDA.

Testifying at a Senate hearing last week, top FDA officials said the agency has accelerated the review of drug applications and instituted new review procedures. The Kassebaum bill would erode the agency's standards and prolong the agency's drug approval, FDA Commissioner David Kessler said at the hearing.

Several observers noted that opposition from the Administration as well as the absence of a corresponding House measure creates uncertainty for the Kassebaum bill (S. 1477). Kassebaum is chairman of the Committee on Labor and Human Resources.

For cancer constituencies, the bill appears to address a variety of problems, some of which have been under discussion for a decade or longer.

The most controversial aspect of the bill is its attempt to set a time limit for review of an NDA. Under the legislation, by 1998, high priority drugs would have to be reviewed within 120 days, while lower priority drugs would have to be reviewed within 180 days.

If these deadlines aren't met, "hammers" would fall. Thus, if a drug is approved in the European Union, it could, by default, be given approval in the US. If FDA is unable to meet approval deadlines, the process could be handed over to a third party reviewer.

Also, the bill addresses the issue of the use of cancer drugs for off-label indications by incorporating the language of another measure, written by Sens. Connie Mack (R-FL) and Bill Frist (R-TN). That measure would remove the FDA policy of prohibiting drug companies to distribute scientific articles on off-label uses of drugs.

FDA: Bill Would Prolong Review

Testifying before the committee, FDA Commissioner Kessler said the bill would in effect prolong the drug approval process.

"If we say that there is an absolute time frame of four to six months, what I believe will happen is one of two things," Kessler said. "First, people would sign off and lower standards, and, potentially, put the country in a dangerous situation.

"I don't believe well-trained reviewers will do that. I think if there is a problem with an application, that application is going to get turned down. [This] will add cycles to the review process."

Transferring an application to outside reviewers would not be a practical solution, either, Kessler said.

"Companies would be faced with having reviews performed by a third party reviewer who has very little knowledge of the specific development process," Kessler said. "The contracting requirement [in the bill] assumes that well-trained staff, free of conflicts of interest, yet familiar with the regulatory review process will be readily available to perform this work. We doubt whether that would be, in fact, the case."

Accepting regulatory approvals of other countries could pose problems, too, Kessler said.

"Assuming that a drug marketed in the European Union should be marketed here simply because of the passage of time places an extraordinary faith in an untested, unevaluated system still in its infancy," Kessler said. "I believe that if we miss a deadline, we should be held accountable.

"Perhaps, this application should then go to an advisory committee. I think that's much more in the public interest than just saying that we will accept by default the results of another country," Kessler said.

EPO In a Box

Seth Rudnick, chairman of the public affairs committee of the Leukemia Society of America, disagreed with Kessler's characterization of the

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European approvals system as inferior to FDA's.

"European approvals are done by very sophisticated agencies," Rudnick, who was involved in the development of Erythropoietin and Interleukin-2, said at the hearing.

Thus, both EPO and IL-2 received approval in Europe a year before they were approved in the US, Rudnick said. Not only that, but the European system required far less paper. While the US NDA for EPO was about 200,000 pages long, the European submission was more streamlined.

"I could literally pick it up in one box," Rudnick said.

Once oncology drugs are approved, frequently sponsors apply for Supplemental New Drug Applications, only to find that at times FDA takes longer to process SNDAs than NDAs, Rudnick said.

"[Review of SNDAs] could go incredibly quickly if you were to add a separate portion of the agency working solely with SNDAs to examine and evaluate peer reviewed quality articles [supporting supplemental indications]," Rudnick said.

Education or Promotion?

The bill's provisions on exchange of information on off-label indications goes beyond the changes that have been requested by cancer patients and physician groups.

The bill would allow drug sponsors to distribute unabridged copies of articles published in peer reviewed journals and chapters from books written by experts in a disease and published by organizations independent of the pharmaceutical industry.

Exchanges of information on off-label uses of drugs and devices would also be permitted in the context of disease management or practice guidelines programs. Also, health professionals would be allowed to exchange accurate summaries of information, the bill states.

The bill also creates a mechanism for approval of supplemental indications for drugs and devices "if experts qualified by scientific training to evaluate the safety and effectiveness of drugs and devices conclude that a new use... represents sound medical practice, based upon reliable clinical experience and other confirmatory information."

A drug sponsor would be allowed to seek a supplemental indication if a new use "has existed in clinical practice for at least five years, is common among physicians experienced in the field, and represents reasonable medical practice, based upon reliable clinical experience and other confirmatory information."

"This provision moves us away from the accepted scientific standard of evidence back toward evidence based solely on anecdotal experience," Kessler said in his testimony. "When drug companies can promote their products' unlabeled use, in the end it's reducing the effectiveness standard."

Off-Label Uses Are Standard

Ellen Stovall, executive director of the National Coalition for Cancer Survivorship, said cancer patient groups and professional societies have been protesting FDA's efforts to prevent drug sponsors from distributing materials on off-label indications since 1991, the year the agency began to enforce these restrictions.

"Apparently, movement by FDA can only be achieved through legislation," Stovall said. "NCCS is very pleased that Sen. Kassebaum has included in her bill the Mack-Frist language that addresses this problem. We strongly urge the committee to support inclusion of such a provision in FDA reform legislation."

FDA's position on off-label indications notwithstanding, off-label use of cancer drugs is commonplace, said Bruce Chabner, clinical director of the cancer center of the Massachusetts General Hospital and chief medical officer of the Dana Farber Cancer Care System.

"If you were to use package inserts as the basis for practicing oncology you would be at a total loss as to how to use drugs," said Chabner, former director of the NCI Division of Cancer Treatment.

In fact, NCI's Physician Data Query system is probably one of the most frequently consulted sources of information on off-label uses of drugs, Chabner said.

"If you had a system that allowed physicians to get those articles from the companies as they are cited in PDQ, I think you would be doing the practicing physician and the patient a favor," Chabner said at the hearing.

"Physicians in general are not that computer-competent that they can find something in a journal that was published three or four months ago. It's just not practical," Chabner said.

"I am involved in clinical practice and research on a daily basis, and I can't keep pace with what's

published even in the best journals. And I doubt that practicing physicians in private practice can do that, either," he said.

In pediatric oncology, off-label uses of drugs are even more commonplace than in treatment of malignancies in adults, testified Gregory Reaman, chairman of the department of hematology and oncology at Children's National Medical Center in Washington.

"If physicians were restricted to using anticancer agents for the purposes approved by FDA, the success of pediatric cancer treatment would not be what it is today," said Reaman, head of the public issues committee of the American Society of Pediatric Hematology/Oncology.

"My colleagues in pediatric oncology and I believe that the risk of receiving inaccurate or incomplete information from the [drug] companies is greatly outweighed by the risk that potentially life-saving therapeutic options may not become known in a timely fashion to those who are treating people with cancer," Reaman said.

Kennedy: Peer Review Is Not Enough

"Even under the current rules, widespread off-label prescription of some products has led to thousands of excess deaths in recent years—deaths that were not detected until adequate studies were carried out," said Sen. Edward Kennedy (D-MA), ranking Democrat on the committee. "This legislation would make that situation worse.

"The proponents of this change argue that restricting promotion to articles in peer-reviewed journals will provide adequate quality control," Kennedy said in his submitted statement. "But this suggestion flies in the face of what is known about peer-reviewed articles and promotional practices.

"Journal articles are powerful promotional tools, but most of them fall far short of meeting the standards of safety and effectiveness that American have the right to expect," Kennedy said.

NBCC, ACS To Submit Views on the Bill

Two major cancer constituencies, the National Breast Cancer Coalition and the American Cancer Society, though not represented at last week's hearing, are sending detailed responses to the Kassebaum proposals, **The Cancer Letter** has learned.

For NBCC, the statement would represent an important milestone since until now the nationwide umbrella group of breast cancer organizations has not been deeply involved in FDA issues.

NBCC president Fran Visco said to the coalition's position on FDA reform would be on the agenda at a board meeting next week.

"We feel that whenever discussion turns to FDA reform, all we have been dealing with is conclusions," Visco said to **The Cancer Letter**. "Some people said FDA is good. Other people said FDA is bad. So, rather than accept other people's conclusions, we decided to get our own data.

"I have been spending a great deal of time trying to make sense of various positions," Visco said.

Following the NBCC board meeting, the coalition plans to release its response to the Kassebaum bill, Visco said, declining to discuss the details of the position NBCC would be likely to take.

ACS, too, is in the process of drafting a response to the Kassebaum legislation, said Susan Polan, the society's director of government relations. ACS is a member of the Patients' Coalition, a group that has been seeking to defend the agency from its critics.

ACS Challenged To Clarify Position On FDA Reform

At a Senate hearing last week, a spokesman for an umbrella group that includes the American Cancer Society presented testimony that suggested the existence of a rift dividing cancer advocacy groups.

A witness who represented the Patients' Coalition, a group that includes ACS and advocates for patients with AIDS and rare diseases, opposed legislative change at FDA.

Meanwhile, a witness for the National Coalition for Cancer Survivorship, along with several prominent oncologists, called for legislative reforms at the agency.

The disagreement in the testimony of Derek Link, of the Patients' Coalition, and Ellen Stovall, of NCCS, was noted in a story in The Wall Street Journal Feb. 22.

At the hearing last week, Link's testimony appeared to echo the statements of FDA Commissioner David Kessler.

"We are very concerned in the legislative solutions that may open up the Pandora's box of competing interests," said Link, assistant director for treatment information and advocacy at Gay Men's

Health Crisis, a group based in New York. "It seems like some of the changes that have been proposed [in the Kassebaum legislation] are already within FDA authority."

Stovall, by contrast, called for legislative intervention. "These are moderate, thoughtful proposals that can be worked with," she said of the Kassebaum bill.

"People with cancer have a right to be involved in treatment decisions on all levels," she said. "Unfortunately, we have been repeatedly disappointed with the polite but unsatisfactory responses [from FDA]. All too often the agency fails to follow through in a satisfactory manner."

While ACS views on FDA reform were not presented directly at the hearing last week, the society is among the 50 groups that formed the Patients' Coalition.

ACS is the only cancer organization in the coalition, documents submitted by Link indicate.

"There is not a rift between the cancer groups in any way," Susan Polan, ACS director of government relations, said to **The Cancer Letter** following the hearing.

"We are supportive of the safety and efficacy standards for FDA," Polan said. "This may require legislative or agency reform. We are working with all the players to assure that that happens."

Polan said ACS is setting forth its position on FDA reform and plans to submit the document to the Senate Committee on Labor and Human Resources next week.

Stovall said she would welcome a clarification of the ACS position on the bill.

"The testimony by the Patients' Coalition clearly suggested that there was a rift between cancer organizations," Stovall said to **The Cancer Letter**. "This issue points out how important it is for all of us in the cancer community to say what we mean and mean what we say."

Samuel Turner, an attorney with the Washington firm of Fox, Bennett & Turner who is also counsel to NCCS, said membership in the Patients' Coalition appears to be inconsistent with advocating FDA reform.

"Regardless of the intent, the position of the Patients' Coalition has been characterized as firmly opposed to legislative reform," Turner said. "Therefore, it is difficult to reconcile support for legislative reform with membership in the Patients' Coalition."

In addition to clarifying its position on FDA reform, the ACS letter is expected to reiterate that the society supports dissemination of peer reviewed materials containing information on using drugs for off-label indications.

One of the principles for FDA reform contained in the Patients' Coalition states that "while validation and third-party reimbursement of non-FDA approved (off-label) uses of drugs are of critical importance to people with serious or life-threatening diseases, the promotion or validation of such uses must not entail a reduction in efficacy standards...

"While the US Department of Health and Human Services should accept the responsibility to establish medical practice standards and third-party reimbursement guidelines, it would be a mistake to focus such mechanisms solely in the context of FDA reform. While the FDA should encourage sponsors to submit supplemental approval applications, research to validate off-label uses remains the responsibility of industry, government and academia."

Tamoxifen Listed In IARC Monograph As A Carcinogen

Tamoxifen reduces the risk of contralateral breast cancer in women diagnosed with the disease, but also increases the risk of uterine cancer, a board of scientists convened by the International Agency for Research on Cancer concluded in a report last week.

The IARC Working Group included tamoxifen in Volume 66 of the Monographs on the Evaluation of Carcinogenic Risks to Humans, because there is "sufficient evidence in humans of the carcinogenicity of tamoxifen in increasing the risk of endometrial cancer," the report said.

Tamoxifen, trade name Nolvadex, is marketed in the US by Zeneca Inc., of Wilmington, DE. A generic version is distributed in the US by Barr Laboratories, of Pomona, NY.

California Listing A Possibility

The IARC, an arm of the World Health Organization, brought together 17 scientists from eight countries to review the evidence on the cancer-causing potential of 14 pharmaceutical agents, including tamoxifen.

IARC said the listing should not be used as a basis for regulatory action.

The IARC's decision could result in the state of California putting tamoxifen on the list of chemicals "known to the state to cause cancer," a requirement of Proposition 65, approved by state residents in 1986.

The state may put carcinogens on the list if its Cancer Identification Committee or another "authoritative body" concludes that a chemical causes cancer.

Last year, the CIC unanimously concluded that tamoxifen should be placed on the list.

However, the California Office of Environmental Health Hazard Assessment decided to delay tamoxifen's listing, and held two days of hearings during which oncologists and officials from Zeneca opposed the listing.

"The mere fact that the IARC rendered a listing would be enough for us to list it, under the 'authoritative body' mechanism," George Kostyrko, a spokesman for the Office of Environmental Health Hazard Assessment, said to **The Cancer Letter**. "We are waiting for the CIC to make a decision."

The earliest the committee could meet would be May, Kostyrko said.

Since 1990, California has listed tamoxifen under Proposition 65 as a developmental toxicant, which requires a warning that the agent may be toxic to pregnant women.

IARC: Risk "Far Lower" Than Benefits

In its report, the IARC said women should not stop taking tamoxifen for breast cancer treatment on the basis of its findings.

"It is important to recognize that the findings of the Working Group do not invalidate the conclusions by clinical oncologists and surgeons that tamoxifen is a very important drug which substantially increases the survival of patients with breast cancer," the IARC report said.

"No woman being treated for breast cancer should have her treatment stopped because of the conclusions of the Working Group.

"The risk of endometrial cancer is far lower than the benefits women with breast cancer receive from tamoxifen," the report said.

"However, it is important that women have access to scientific opinion on the low risk of endometrial cancer, so that they can make an informed decision on the treatment they will accept."

In a statement Feb. 21, NCI said the IARC report reaffirmed the benefits of tamoxifen as a treatment for women with breast cancer.

"The information reviewed by the IARC Working Group is not new information," the Institute said. "NCI has previously reviewed the same data and has already taken this into consideration in the study designs and informed consent procedures in all tamoxifen clinical trials, including the Breast Cancer Prevention Trial.

"Women who are taking tamoxifen as treatment for breast cancer should be assured of the benefits of the drug, which were reaffirmed in the IARC report," the statement said.

NCI noted that in previous reports, IARC classified as carcinogens several other hormonally related agents, including oral contraceptives, estrogen replacement therapy, and steroidal and nonsteroidal estrogens.

Karen Miller, a spokesman for Zeneca, said the data the IARC reviewed is included in the product labeling for tamoxifen.

Foundation Seeks Applicants For Cancer Therapy Projects

The Cancer Treatment Research Foundation, a non-profit, 501(c)3 organization, is accepting applications for new and pilot/feasibility projects in the areas of innovative cancer therapy and nutritional oncology.

These areas include new applications of conventional anticancer therapy, biological response modifiers, immunotherapy, gene therapy, quality of life, nutrition, and bionutrition.

The initial, first phase application will be in the form of a two or three-page concept proposal including background, rationale, study design, budget and significance of project in relation to the overall mission of CTRF.

The concept proposal will be reviewed by selected members of the Board of Scientific Counselors of CTRF. Investigators whose preliminary proposals are approved by the board will be invited to submit a formal application.

Applicants should send letter of intent to: Denis Miller, Scientific Director, Cancer Treatment Research Foundation, 3455 Salt Creek Lane, Suite 200, Arlington Heights, IL 60005. Applicants may call Gary Anderson, tel: 847/342-7430 to confirm an intent to submit an application.