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An "Insurgency" Targets Randomized Trials, Demands Access To Investigational Drugs

By Paul Goldberg

Perhaps it would have been prudent of the Food and Drug Administration oncologist Richard Pazdur to deflect the Congressman's question.

Yet, there it was: an opportunity to lean toward the thin, black microphone on the witness table and reduce a messy situation to a maxim.

What was the problem with Erbitux, the monoclonal antibody so scandalously mishandled by ImClone Systems Inc.?

"It's called good drug, bad development plan," Pazdur said at the June 13, 2002, hearing of the subcommittee on oversight and investigations of the House Committee on Energy and Commerce.

Surely, it seemed that this would be a hard point to misconstrue: Erbitux was "good," because it had been shown to shrink tumors. The company's development plan was "bad," because it failed to show convincingly how often tumor shrinkage occurred and why. There was no way for Pazdur to foresee that these words would identify him as a target of opportunity in a half-century-long battle over the criteria for approval of cancer drugs.

A clinical researcher who took a six-figure pay cut when he left M.D. Anderson Cancer Center to join the chronically cash-starved federal agency, Pazdur had no part in the decision in 2001 to bounce Erbitux back to ImClone. He hadn't seen the company founder Samuel Waksal until earlier that morning, when the gaunt executive stood up to take the Fifth amid an explosion of photo lights and flashes.

Yet, thanks to these words, Pazdur came to the attention of the editorial board of The Wall Street Journal. For decades, the Journal's editors advanced the view that the 1962 amendments to the Food, Drugs and Cosmetics Act placed an unnecessary burden on the industry by demanding that pharmaceutical companies demonstrate that their products are effective in fighting disease. Instead of helping patients, these requirements stifled innovation and did harm, the Journal argues. Before the efficacy requirement, drug approval was limited to a certification of safety. In oncology, the Journal advocates the view that the terminally ill should be free to take barely-tested remedies outside clinical trials.

"As FDA oncology drug chief Richard Pazdur noted… with refreshing candor, Erbitux is a case of 'good drug, bad development plan.' In other words, the company hadn't jumped through the right hoops," the newspaper said in an editorial published on Oct. 10, 2002, the day of the subcommittee's second hearing on ImClone. "[The] agency apparently wanted to 'send a message' about the importance of doing sufficiently rigorous trials, as if this were

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Publication Break:
The Cancer Letter takes its annual summer publication break for the next four weeks. The next issue is scheduled for publication on Sept. 9. The Cancer Letter is published 46 times a year.

WSJ Editorial Page Leads Assault On Efficacy Standard

(Continued from page 1)

just another antihistamine, not the last hope for dying patients. That's the real ImClone scandal."

So, doctor, if you *know* that Erbitux is good, why didn't you approve it? This rhetorical gotcha was so clever that the Journal has repeated it on many occasions, most recently on July 6, three years after the ImClone hearing.

Wasn't it the responsibility of the company to demonstrate that Erbitux is safe and that it helps patients?

"It seems to me that as long as it's obvious to the right-thinking people that something is an effective drug, it ought to be on the market even if the study hasn't been perfect," said Robert Pollock, the Journal editorial writer whose commentary on FDA made him a finalist for the 2003 Pulitzer Prize. The agency was complaining "about the quality of the data vis-à-vis artificial and unnecessary endpoints that they themselves have created," Pollock said.

Pazdur's name has become the stuff of headlines on the Journal's editorial pages: "Pazdur's Revenge"… "Pazdur's Cancer Rules"… "Pazdur is What the Doctor Ordered."

The newspaper describes the oncologist as a "hyper-cautious" man of "anti-industry views" who insists on costly and unethical placebo-controlled trials, and is determined to use mind-numbing minutiae to drive American's cancer sufferers into the grave by denying them access to life-saving drugs.

The editorial writer Pollock says none of this is personal. "It's not that I am guessing what he is up to. He is quite frank about his views," Pollock said. "Look, the bottom line is, policy is made by people. I try not to criticize Pazdur as a human being. I criticize his policies."

The bull's eye on Pazdur's forehead grew bigger earlier this year, when the agency, taking directives from the House Committee on Energy and Commerce and ignoring the Journal's campaign, combined the drugs and biologics divisions and placed Pazdur in charge of the new entity, the Office of Oncology Drug Products.

The anti-efficacy movement has been around for nearly half-a-century, but in recent years it has grown to include groups that demand faster advances in medicine and seek "modernization" of FDA. The Journal has become a platform for a loose alliance, which includes the financier Michael Milken, the Abigail Alliance for Better Access to Developmental Drugs, the Washington Legal Foundation, the Manhattan Institute, the American Enterprise Institute, the Cato Institute, and the Competitive Enterprise Institute. The goal—stated in the Journal editorials—is to set policy for the Republican Party and the Bush Administration.

Steven Walker, an environmental engineer and author of a plan by the Abigail Alliance to give patients access to investigational therapies as early as after completion of toxicity testing, describes this movement as "an insurgency," adding that he is reluctant to borrow the term currently reserved for Iraqi assassins and suicide bombers. Walker, whose wife died of cancer, characterizes Pazdur as a "reactionary," a "Neanderthal from a scientific standpoint," an "incompetent scientist and regulator," and a "narrow-minded bureaucrat" whose "tunnel-vision" is responsible for the deaths of "tens of thousands every year."

Mainstream oncologists, experts in clinical trials, and patient groups that support Pazdur describe this campaign as an effort to reduce the drug approval process to perfunctory rubber-stamping of unproven remedies, which would then be dispensed without reliable methods for assessing cost, benefit, physical harm, and the loss of life.

"The vehemence and invectives toward Rick are just stunning to me," said David Johnson, deputy director of the Vanderbilt-Ingram Cancer Center and former president of the American Society of Clinical Oncology. "I just really don't understand it. He's become a symbol."

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Member, Newsletter and Electronic Publishers Association

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
Customer service FAQ: www.cancerletter.com

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Academic oncologists view Pazdur as their peer, a member of an elite stratum of clinical researchers, regulators, and industry scientists who develop, test, and review cancer drugs.

"The truth of the matter is that Dr. Pazdur is exactly what one would want at the helm of the oncology office at the FDA, a bona fide oncologist who has done well-designed, well-conducted, meaningful clinical research," said Johnson, a former member of the FDA Oncologic Drugs Advisory Committee, a group of outside experts that the agency consults on clinical questions. "I can't imagine that you would want someone who has not done that. There is not much doubt that part of what we are seeing here is an attack on science itself."

Opponents of clinical trials are trying to bring back the days when medicine was practiced based on the opinion of esteemed professors rather than on the results of clinical trials, said George Sledge, co-director of the Indiana University Cancer Center, chairman of the breast cancer committee of the Eastern Cooperative Oncology Group, and a former member of ODAC.

"We can't ignore the last 50 years of medical research," said Sledge. "The difference between being a doctor and being a witch-doctor is the use of evidence-based medicine."

Otis Brawley, professor of hematology, oncology, and epidemiology at Emory University, associate director for cancer control at Winship Cancer Institute and a former ODAC member, describes Pazdur-bashing as a return to a "time-honored tradition."

"When science contradicts dogma, scientists risk getting burned at the stake," Brawley said. "That's basically why these folks are trying to dispense with Dr. Pazdur. But history tells us that scientist-burnings do not alter the laws of nature."

Patient groups that advocate rigorous clinical trials stand poised to defend Pazdur, said Ellen Stovall, CEO of the National Coalition for Cancer Survivorship. "We strongly disagree with the view that lowering the efficacy and evidence-based standards for approval of new cancer drugs is a viable strategy," Stovall said. "Also, I find the personal disparagement of Dr. Pazdur to be totally misdirected.

"Over the past five years, Dr. Pazdur has championed a more transparent and coordinated approach to oncology drug and biologics review at the FDA," said Stovall, who lobbied the agency to place Pazdur in his current job. "He consistently seeks opportunities to garner input from patient advocates and clinicians to address problems with the system without ratcheting down the evidence base for approving new drugs. He has our support."

Pazdur, 53, is hardly the FDA equivalent of Che Guevara. A bespectacled man of medium height, he wears navy Brooks Brothers suits, moves with a runner's gait, and appears to enjoy verbal sparring over data. Friends describe him as a church-going Catholic of no discernible political affiliation. Far from being an enemy of the pharmaceutical industry, he has spent decades developing compounds for drug companies.

Pazdur declined to be interviewed for this story. "I am always delighted to discuss science," he said.

Tilting at Efficacy

The Journal editorial writers have high regard for another oncologist, Robert Oldham.

Years ago, Oldham built a company around the premise that every tumor is unique and every therapy should be unique, too. FDA should limit itself to certifying the safety of cancer drugs, and leave it to qualified clinicians to determine effectiveness, Oldham argues. The editorialists like Oldham so much that they have proposed that someone like him should run FDA in the Bush Administration.

The Journal has been following Oldham for two decades. On Dec. 16, 1985, the newspaper slammed the National Cancer Institute for not offering broad access to its trials of interleukin-2 lymphokine activated killer cell therapy. In the same editorial, the newspaper applauded the former NCI scientist Oldham for starting Biotherapeutics Inc., a company that made LAK-cell therapy commercially available.

"Clearly, the patients paying for treatment at Biotherapeutics are assuming a personal and financial risk; some cancers haven't responded at all to LAK-cell therapy," the Journal said. "But surely there are informed cancer patients in this country who want nothing more than to assume that risk."

The conclusion of that 20-year-old commentary would fit seamlessly into the newspaper's current criticism of the agency: "If the research and regulatory community doesn't consider some way of adapting itself to speed up patient-access to promising therapies, then cancer curators shouldn't be surprised if sick people soon start assaulting a system that, for all its achievements, prescribes little more than patience."

In 1987, a Wall Street analyst projected that Biotherapeutics would generate $385 million in revenues in 1992. Instead, the company failed to attract enough patients willing to pay $35,000 per treatment with IL-2. In 1990, Oldham was ousted by the board, and Biotherapeutics became Response Technology Inc.

In its second life, the company offered bone marrow transplants and high-dose chemotherapy for breast cancer, a treatment that ultimately fell victim to data from randomized clinical trials.

Oldham spent some time in South Carolina, running that state's biotechnology association. Now he works at a hospital-based practice in Thomasville, a southern Georgia town of 20,000, where he practices what he describes as "plain, standard, garden-variety oncology," consulting, and writing novels and opinion pieces for the Journal.

"As I get older, I am doing less and less personal experimental work, because it's very difficult to access capital," he said in an interview recently.

Oldham, 63, describes himself as "Don Quixote" of the movement to repeal the efficacy requirement. "You can recognize pioneers by the holes in their back," he said recently. "I've got a few." His prognosis for the movement is bleak: "People that believe in government as nanny really believe that FDA is doing a great job of protecting us."

Experimental drugs should be widely available for use outside clinical trials by the time toxicity studies are completed, Oldham said. "I don't think any cancer patient ought to die for lack of having access to a phase II cancer drug," he said.

What's the benefit of giving an untested therapy outside clinical trials?

"The benefit is, the responding patients would be alive instead of dead," he said. "You can't treat a dead cancer patient. I don't know of a single cure of a dead patient. That's the problem."

How would these patients assess the risks of taking an experimental drug that has been studied only in toxicity trials and is entering phase II testing?

"I am not worried about the toxicity in patients that have a few months to live," Oldham said. "The basic fact is that cancer patients are being protected to death. They just want to try something and hope for the best."

Randomized clinical trials waste lives for the sake of obtaining data, Oldham said. "This concept that somehow society's needs are more important than an individual's needs is just contrary to everything this country was built upon," he said. "This country is built on the individual. Communist countries are built on collective societies being the driving force. People who get sick want to have a chance to stay alive and get well.

"Most human beings operate on a personal benefit level, not through altruism. Altruism, I think, is a fairly rare and overrated event. When they are denied access to stuff and they go ahead and die, it's just a shame."

In the ideal world, randomized trials would be rare, Oldham said. "Look at surgery as a good example," he said. "Surgery is a profession built on the individual patient and the observations of physicians. They don't always get it right, but there are very few sham surgeries to randomize against."

Historical data may be good enough for determinations of efficacy, Oldham said. "Basically, you build up your database by the experience of physicians in clinics and hospitals, and you look at historical controls," he said. "FDA would say historical controls are not accurate. They are not as accurate as randomized controls, statistically, but they may be a perfectly good way to develop drugs by allowing far more people to get the drug than do now in a shorter period of time to answer the question."

In the ideal world, one may be able to make a case for a conducting a randomized trial when two regimens appear to be similar in phase II trials, Oldham said. In those trials, patients should be paid for submitting to experimentation. "You would advertise and reward people for their gift to society," Oldham said.

Oldham said he still believes that every patient's cancer is unique. "That's been my thesis forever," he said. "It's so intuitively obvious that if everybody's genetic program is different—other than identical twins—how can their cancers be alike?

"Their cancers are nothing more than a manifestation of their genetic program. If you get cancer and I get cancer, why should our cancers be the same when our whole genetic program is completely different and the cells are active based on our genetic program? There is just no logic to that."

These views, controversial two decades ago, place Oldham even further from the mainstream today. "To say that each person's cancer is unique is an exaggeration and doesn't fit with the data," said Ronald Herberman, an immunologist and director of the University of Pittsburgh Cancer Institute.

"What it would lead to is to pursue an entirely customized treatment approach for each patient, which is what Dr. Oldham has built a company around," Herberman said. "The main problem with that is that this is likely to lead to a very expensive approach to treatment, because every individual is going to need a customized vaccine. That might be justifiable if it's clearly superior to the alternatives, but that comes down to what are the alternatives and how good are the data to say that this individualized approach is superior."

While some hematologic malignancies—

particularly lymphomas—have unique characteristics in every patient, solid tumors don't.

"Outside of B-cell and T-cell malignancies, there is no scientific evidence that would support an individually specific difference," Herberman said. "Even with those tumors, some idiotypic determinants have been found to be shared among different tumors."

There is no evidence to suggest that vaccines for the treatment of lymphoma would be superior to the new generation of agents: the monoclonal antibody Rituxan, as well as its radio-labeled versions, Zevalin and Bexxar, Herberman said.

In solid tumors, the picture is even clearer. "The identification of molecular targets has led to sub-setting of patients, producing no evidence that each patient requires a uniquely specific form of treatment," Herberman said.

"If Dr. Oldham extends his argument to solid tumors, as far as I can tell, he stands alone."

Surprise Endorsements

In an opinion piece published in the Journal Feb. 2, 2001, Oldham attacked FDA for imposing burdensome regulations on the industry and reflected on his achievements as a pioneer of medicine.

"We are now on the verge of realizing the scientific opportunities of the genome project," he wrote. "Unfortunately, our regulatory book is many pages longer than the book of life."

The Journal editors accompanied the piece with an attack on the efficacy standard and an endorsement of Oldham for the job of FDA Commissioner. Citing an industry estimate, the editorial said that it cost $500 million to develop a drug, and "most of that $0.5 billion is spent proving 'efficacy,' that a drug will perform as claimed, using massive placebo-controlled clinical trials.

"This crude massiveness, with its indefensibly high costs, is increasingly inappropriate to the scientific and economic realities of modern drug discovery and needs to be rethought. "

According to the Journal, Oldham has a unique understanding of this problem:

"Back in the 1980s, Dr. Oldham tried to circumvent many of these impediments with a firm called Biotherapeutics, which let patients pay privately for cancer therapies based on this new science," the editorial continued. "Dr. Oldham may have been ahead of his time, but successor companies today are trying to bring these benefits to patients…

"The Bush folks would do well to talk to someone who understands these realities. Then put someone like that in charge of reforming the FDA."

Oldham said he wasn't interested in the top job at the agency and didn't seek endorsement.

"I didn't even know they were going to do that, " he said. "They did that totally on their own, which I though was kind of cute, because there is no chance of somebody like me becoming head of the FDA, because I am viewed as contra to FDA.

"I would never have taken the job, because I can't afford to work there. My lifestyle had gotten too expensive for me to work for the government again. That job only pays about $130,000-$140,000 a year."

A month after the Journal's endorsement, on March 6, 2001, The Washington Post reported that someone from the office of Sen. Strom Thurmond (R-SC) had called the White House and said that getting an administration job for Oldham was one of the Senator's top priorities.

Also, a letter on Thurmond's Senate stationery requested that a White House official give "prompt attention and assistance" in scheduling an appointment for Oldham. According to the Post, the handwritten letter concluded: "Please call Nancy and me at home not at the office concerning this matter. Highest personal regards, Strom Thurmond."

Oldham said no lobbying took place. "I had a relationship at one point in time with Nancy Thurmond, who was the wife of Strom Thurmond, and I think, because she and I were an item for a while, people thought that somehow that was part of the deal," he said. "She didn't do any lobbying, but people imagine all kinds of stuff, you know."

The Journal Picks Bayesians Over Frequentists

Recently, the Journal proposed a plan for development of cancer drugs:

"[It's] time for Congressional action mandating that the agency use 21st-century science and statistical methods to get therapies to patients sooner," the newspaper said in an editorial March 29. "More specifically, drug approvals could be based on large trials open to all comers and analyzed with so-called Bayesian statistics, as already happens in the FDA's medical device division. (Yes, the agency at least recognizes that studies involving, say 'placebo' defibrillators would be beyond the pale.)"

Weeks before this proposal surfaced in the Journal, Scott Gottlieb, then resident fellow at AEI, mentioned something similar in an investment newsletter he wrote for Forbes. Gottlieb was a senior policy adviser to the

former FDA Commissioner Mark McClellan.

The agency should make better use of modern mathematical tools "for using data about new drugs that is not 'randomized,' or randomly compared to a placebo, but derived from large populations of patients all being given the same treatment," Gottlieb wrote in a column Feb. 18.

"This kind of 'dirty data' involves a mathematical science called Bayesian statistics that allows statisticians to glean strong conclusions off large population data, just like economists do. This is another science that is poorly developed inside FDA."

Last week, Gottlieb returned to FDA as deputy commissioner for medical and scientific affairs. This White House appointment makes him a top-ranking physician at FDA.

The Journal writer Pollock acknowledges that he is not an expert in "math." Bayesian methodology "is being described to me as a way to derive meaningful and full conclusions from so-called 'dirty data.' It's often used by economists," he said.

The Journal's plan is based on a fundamental misunderstanding of Bayesian methodology, said Donald Berry, chairman of the Department of Biostatistics at M.D. Anderson Cancer Center and a leading proponent of using this methodology in cancer trials.

"I am chagrined by using Bayesian approach inappropriately," said Berry. "It casts a shadow over the approach."

Bayesian methods are founded on the work of Thomas Bayes, an 18th century British theologian and mathematician. Bayes' theorem established a mathematical basis for testing the correctness of beliefs. Recent advances in computer technology make it possible to make the multitude of calculations needed to use this method in clinical research.

"It is not the kind of thing that suddenly you become Bayesians and you don't have to do randomization," Berry said. "The Bayesian approach is not a different scientific principle. It's a way of handling information, it brings to the fore all the information that's available, but it doesn't mitigate the need to do randomized trials."

Testing a drug, a "frequentist" statistician may assume that he knows nothing about how the drug would perform, or may structure the trial to prove himself wrong. The frequentist's trial would specify when the data should be analyzed, and would have strictly enforced rules for stopping the study.

A Bayesian would use the trial to test his "prior belief," and would incorporate new information as it emerges. Under this approach, drug doses could be changed, and trials can be stopped at the point when researchers become convinced that they have the answer. "It means that Bayesian randomized trials can be smaller," said Berry, who is also a faculty biostatistician in the Cancer and Leukemia Group B.

However, a Bayesian has to be careful about what he thinks he knows, Berry said. Historical data in cancer change constantly, as diseases are influenced by early detection, treatment, or some unexplained events. These changes make historical controls unreliable.

"Some diseases are changing incredibly rapidly," Berry said. "I design trials in breast cancer for CALGB, and I make the same mistake every time I design a trial. You'd think I'd learn. I use information from previous trials that we've conducted in the disease to do power calculations, to estimate what's going to happen in the next trial, and I am always wrong. I always overestimate what the number of events will be. If you look at one trial to the next, to the next, in the same patient population, say node-positive breast cancer, the prognosis is getting better, and better, and better. It is becoming more difficult to conduct trials because of that, because the event rates are now so low, but it means that if you are going to try to use historical data, you've got problems because of that change."

The differences between the Bayesian and frequentist approaches are philosophical rather than practical, said Stephen George, director of biostatistics at the Duke Comprehensive Cancer Center, director of the CALGB statistical center, and a member of ODAC. "Recognizing that there is a sharp philosophical difference between these approaches, there often is not a sharp practical difference," said George, who is not a Bayesian. "As data start coming in, these approaches get closer together, and if you get enough data, it tends not to matter."

Bayesian methods have been accepted at FDA. About 10 percent of new medical device applications approved by the FDA Center for Devices and Radiological Health are based on Bayesian designs and analyses. However, many of these devices are approved on the basis of *randomized* Bayesian trials, Berry said. Also, at least one drug—Bristol-Myers Squibb's Pravigard Pac—was approved based on Bayesian analyses of efficacy. Pravigard is used to slow the progression of atherosclerosis and to reduce the risk of heart attack, stroke, and transient ischemic attack.

"With any treatment short of a cancer cure, we would be lost without randomization, and the really sad aspect is that we would have lots of patients being treated with things that have negative side effects that

are doing them no good," Berry said. "That's probably the worst travesty."

Berry has used Bayesian methods on Wall Street, too. "There are some people on Wall Street who think that I talk to God, because I get it right," he said. "Actually, I listen to Bayes. This methodology is great for assessing uncertainty, but this isn't the same as asking the question, 'Is this drug better than that drug?'"

When you are setting standards for the practice of medicine, a guess isn't good enough, Berry said.

"When you do the best guess, you assess the uncertainty, and you say that probability is such and such, and you go with the odds, but you are not exposing thousands or millions of people to the result of your guess," he said.

Taking the Next Step

While the Journal portrays FDA as a bumbling, antiquated agency, it has refrained from attacking the discipline of mainstream academic oncology.

Walker, an owner of a Tampa, Fla., company that oversees cleanup of Superfund toxic waste sites, takes that next step. His goal is to separate oncologists from biostatisticians, and he sees only one way to accomplish this: by using the courts and Congress to force FDA to change its current standards of evidence and rely on smaller trials that would not seek to produce statistically significant results.

"The FDA at this point in time has to become the leader," said Walker, who speaks rapidly, often switching to hard-hitting stanzas of a campaign speech. "They have to drag people into this, because if they don't, there are a lot of people who aren't going to go."

Walker has read piles of FDA rules and guidance documents. He has attended many an oncology meeting and gone through stacks of medical literature. Nothing he has seen, read, or heard so far has shaken his belief that oncologists have allowed statisticians to usurp control of their entire discipline.

"Statisticians tell you that you don't learn anything from anecdotal information. That is bull," he said in a recent conversation. "The idea that you have to have a metric, and that you have to have this rigid process that you make everybody follow is fundamentally flawed, because it virtually guarantees that you will make a lot of errors. How many people are we going to kill for the sake of protecting a failed regulatory concept?

"Our whole system, and all the money that runs through it in a big loop, and all the training of everybody, is based on that one little concept that we will follow the rules of statistics, whether it's applicable or not. It's a cult-like belief, because people keep repeating over and over that you can't learn anything about safety and efficacy unless you do a comparative clinical trial."

Walker said he would like to see "smaller and smarter" trials. Scientists would rely on direct observations made in trials designed to confirm reasonable safety and effectiveness rather than establish it statistically. After the drugs are approved, patients would continue to be monitored.

"Statistics is nothing more than a set of mathematical algorithms that are sometimes useful in looking at scientific data," Walker said. "Quite often they are not, and they are to be avoided with every fiber of your being, because all they would do is mislead you."

In the environmental field, statisticians play a secondary role, Walker said.

"We do very similar types of investigations in my field, and when a statistician walks in the room, the scientists cringe, because you are about to do battle with someone who is a functional idiot," he said. "They are going to want you to do something that is going to be of no use to you when it comes time to clean up the site, but they are going to make you do it.

"You are going to spend a bunch of money doing a separate study to satisfy the statistician, and when he is done, he is going to give you a number, and you are going to look at it and say, 'That's of absolutely no use to me. What I need is backhoes, and bulldozers, and pumps, and treatment systems.'"

The Education of Steven Walker

Walker's immersion in the cancer field can be traced to Dec. 28, 2000, the day his wife Jennifer McNeillie learned that she had stage IV colon cancer that had spread to two lobes of her liver.

McNeillie, 45 at the time of diagnosis, spent the following two and a half years in pursuit of treatment options. Seeking the most aggressive care available, she had a surgeon attempt a resection, an unusual move for a patient with disease in both lobes of the liver. In another unusual move a few months later, metastases were removed from McNeillie's ovaries.

First, she tried the Saltz regimen of Irinotecan, 5-fluorouracil, and leucovorin. This produced a partial response—tumor shrinkage of more than 50 percent—but by November 2001, the disease was once again on the move.

"We dropped off the cliff of approved therapies," Walker said. "There was nothing left but capecitabine. There was no second-line therapy, and patients were just dropping off the cliff as a result of that."

In gastrointestinal oncology, capecitabine as a single agent is the end-of-the road. You start capecitabine and contact a hospice.

At this point, McNeillie and Walker knew that two promising cancer drugs—Eloxatin and Erbitux—had failed to get FDA clearance. Eloxatin was rejected following a negative vote by ODAC, and Erbitux was sent back with a "refusal to file" letter, because FDA staff found the application "uninterpretable."

"It was an incredibly stupid, lethal performance by the FDA," Walker said.

He still considers what-ifs. "Had there been Eloxatin available then, had Erbitux become available, her chances of living considerably longer than she did would have gone up dramatically," Walker said. "Her chances of a cure—her chances of living a normal lifespan—would have gone up from about 5 percent to perhaps 15 or 20 percent."

McNeillie and Walker weren't willing to give up. "I was calling FDA on a regular basis, I was calling my senators, I was calling the administration," said Walker. "I was calling and asking to talk to the President. I am not a shrinking violet. And, by the way, if you know what you are talking about, that works."

In December 2001, an FDA official told Walker about a group called the Abigail Alliance. The alliance was founded by Frank Burroughs, a Washington-area engineer, in honor of his daughter, who died of head and neck cancer.

Abigail was diagnosed a year to the day before McNeillie, on Dec. 28, 1999. As her treatment options dwindled, a doctor said that it might make sense to try one of the emerging drugs that blocked the epidermal growth factor receptors, Burroughs said.

He tried to get Erbitux and AstraZeneca's Iressa, but the drugs weren't available either through trials or off-protocol. Abigail's story was covered in The Washington Post and on local and national television, but the coverage didn't help her get the drugs.

Abigail died in her room at her mother's house on the afternoon of June 9, 2001. She was 21, a third-year student at the University of Virginia. Late that night, Frank experienced what he describes as "an epiphany."

He sat at an umbrella table on a small deck behind his house in Arlington. The night was hot and muggy. "My own death would have been a picnic compared to that," he recalled. "Suddenly, out of nowhere, I had an overwhelming sense of peace, and I felt God's spirit and Abigail's spirit around me. A cool breeze came up, and in another second, a thought flashed through my mind, 'There are other people as precious as Abigail.'"

Frank set up an advocacy group in the family room, a step away from the deck. His goal was to help patients obtain investigational drugs. Generally, he refers patients to clinical trials or expanded access programs, and sometimes he tries to convince drug companies to provide the drugs off-protocol. After that fails—which is usually the case—he blasts press releases to his list of 100 to 120 reporters.

"I think the reason we've had such good media coverage is that this is a very compelling story," said Burroughs, 58. "And I've worked hard on it. I never give up on a media contact, unless they block my email or go work somewhere else."

Walker and Burroughs complemented each other. Walker had the vision to spark a rebellion, and Burroughs knew how to work the media. "Frank is a brilliant guy, but he doesn't have my personality," Walker said. "He is not a real aggressive guy, like I am. We went through a three- or four-week process of getting to know one another and deciding whether we could work together. I thought he was too mellow, and he thought I was too crazy."

Though most of the alliance's support comes from the right, both Walker and Burroughs describe themselves as political independents and say that they vote both sides of the ticket.

Looking for Therapies

Walker said his wife was involved in his efforts to pinpoint the flaws in the system of drug approval.

"We'd be driving to chemo, and she'd say something and—boom—light bulbs would be going off over my head," Walker said. "She was living it, she was providing input from the perspective of the patient, and I was doing the nuts-and-bolts stuff of figuring out what was wrong, reviewing the regulations and figuring out what to change."

Why weren't the treatments McNeillie wanted available at the time she wanted them?

"It took me about two hours to figure out what the problem was," Walker said. "It was FDA. It was this rigid, small-minded little agency acting like the Department of Motor Vehicles giving out licenses and license plates," Walker said. "They are typical, narrow-minded, obstructionist regulators."

McNeillie did receive the drugs she wanted. The couple found a clinical trial of Eloxatin and agreed to randomization to one of the trial's three arms.

"Our decision was, we are going to enroll in the trial, and if we don't get randomized to the drug, we are

going to walk away," Walker said. The trial represented the only way McNeillie could obtain Eloxatin at the time, and the control arm would have put her on the drugs she had failed earlier.

By that time, Walker had developed contempt for the system. "Patients are literally thrown away in a clinical trials process," he said. "They are wasted in inferior control arms. They are wasted in placebo control arms. They are wasted outside clinical trials that they can't get into. And the regulatory environment is a system that is aimed to protect the integrity of the process, and the process doesn't have scientific integrity, it doesn't have public service integrity, and it has become a barrier."

Not all patient advocates share this contempt.

"I do not think it is ethical for a person to agree to participate in a clinical trial, knowing and understanding full well that it is randomized, and then pull out if they don't like the arm they are randomized to," said Robert Erwin, who founded the Marti Nelson Foundation, named after his wife, a California physician who died of breast cancer. "I think the ethical problem comes from the damage they do by delaying the trial (which adds costs and delays getting important medical information to help other people), or potentially taking the place of someone who would or could otherwise participate."

McNeillie was randomized to Eloxatin, infusional 5-FU, and leucovorin, the arm she wanted. However, 12 weeks later, the disease progressed, and she was back on the edge of the cliff.

The couple tried to get into a trial of the Abgenix Inc. monoclonal antibody ABX-EGF (panitumumab), but didn't meet the enrollment criteria. In September 2002, when McNeillie was literally on her deathbed, she managed to get Erbitux in a phase II trial.

Two days after she started the drug, the accumulation of fluids stopped, and after six weeks, her tumor burden dropped by 70 percent. "My wife literally went from being on her deathbed to being a full-time worker, going skiing, going hiking, living a normal life," Walker said. "She would say to me, 'I wake up some mornings, and just don't think I have cancer at all.'"

Over six months she was on Erbitux, McNeillie was able to go skiing twice, in Colorado and Utah.

"My anger and frustration with the system was peaking around this time," Walker said. "I am not one of these diplomatic people who are gonna let idiots run wild without saying or doing something about it. FDA was making these massive mistakes, literally pushing people into premature graves. Knowing they were doing it, but not caring, because their tunnel-vision view of how you develop and approve drug has nothing to do with what it does to patients."

After McNeillie's cancer returned, she was taken off the study, and following a seven-week interruption in treatment, got back on the drug under a single-patient exemption created for her by Bristol-Myers Squibb, ImClone's partner in the development of Erbitux.

"The seven weeks she was off had allowed the disease to progress to such a point that she was essentially dead," Walker said. "She lived longer than she would have had we done what we were advised to do on a couple of occasions: call hospice. If we hadn't kept trying, she would have died sometime in the spring of 2002."

By the time McNeillie died—on June 27, 2003—Walker had become a leading theoretician of the movement, the author of a plan called Tier 1.

The plan calls for creating a new category of marketing approval, which would allow companies to sell experimental drugs as early as after completion of phase I trials, provided that patients are unable to get into clinical trials and that physicians are willing to write prescriptions (http://abigail-alliance.org).

The Washington Legal Foundation, a conservative public interest law firm closely associated with the pharmaceutical industry, helped the alliance file a citizens' petition to FDA.

Separately, WLF sued the agency, claiming that constitutional rights of cancer patients to get therapy of their choice were being denied. The case is also about the efficacy standard and the right of pharmaceutical companies to earn "a modest and reasonable profit" on investigational drugs. "[Terminally] ill patients with no treatment options have a right to decide *for themselves* whether to take an investigational drug that the government concedes is sufficiently safe for testing in human subjects," court papers state.

The U.S. District Court for the District of Columbia dismissed the suit, stating that the alliance was in effect requesting "new constitutional rights." The matter is being appealed (http://www.wlf.org).

Articles on the Abigail Alliance court case have appeared in the Journal and in The Milken Institute Review, a publication started by the financier prostate cancer survivor who opposes the efficacy standard for approval of cancer drugs. The piece in Milken's journal was co-written by Walker and WLF Chairman and General Counsel Dan Popeo.

"It's bothered me that this apparently is going to be my purpose in life," Walker said. "It's difficult to do this. It's extremely time-consuming. My wife is

gone. I have not established another relationship. I am so consumed by this, because it needs to be done, and someone needs to do it. It seems like I just happened to be the right person at the right time."

The Journal editorial writer Pollock learned about the Abigail Alliance by reading his own paper. Burroughs was quoted in a news story about expanded access to Erbitux. "Look, I think this is a powerful message, because it cuts across traditional partisan lines," said Pollock, who was given the Abigail Alliance's first media award the year he missed the Pulitzer.

By working with the alliance, the Journal finds real patients to illustrate its arguments. Recent examples include the story of Kianna Karnes, 44, whose inability to get experimental therapy for kidney cancer gave the Journal a springboard for discussion of randomization, the urgent need for modernizing FDA, and the virtues of "so-called Bayesian statistics."

"We've never understood why the Republican majority in Washington hasn't been more active on drug approvals over the past four years," the Journal opined on March 24. "What better way to demonstrate compassionate conservatism and commitment to a 'culture of life'? Or to unite the free-market wing of the GOP with the social conservative one? Finally, what better riposte to the left's equation of support for embryonic stem cell research with support for medical progress?"

Five days later, the editorial page reported that Karnes had died, and urged patients to contact the Abigail Alliance in order to "make their voices heard" and to "educate themselves on the issue."

After reading the Karnes editorials, Emil Freireich, an oncologist at M.D. Anderson, left a note on the alliance's Web site. Freireich, 78, has been skeptical about the value of the efficacy standard and reliance on randomized trials. But more than anything, he resents the agency's Investigational New Drug procedures, which require that a researcher obtain FDA permission before experimenting on patients.

"They can't regulate the interaction between a physician-scientist and a dying cancer patient," said Freireich, whose achievements include making the first platelet transfusions for cancer patients, and developing combination and maintenance chemotherapy. "That is something that is in the area of professional expertise, and they don't know shit about it."

Freireich has little respect for people who work at FDA, and he makes no exception for his former M.D. Anderson colleague.

"You give power to an agency, the agency has to find people who will do this drone work, so they look for failed oncologists, and the failed oncologists love this position, because now they have power," he said. "Look at Ricky Pazdur! He was so-so and not doing much; now he is King Kong! He gets invited to every talk on every drug at every meeting everywhere in the world.

"Who would know what is the highest probability of benefiting a patient and the lowest probability of doing harm? Is it Dr. Pazdur, who's been sitting at a desk for 10 years, or is it Dr. Freireich, who's in the clinic, beating his ass, taking care of dying cancer patients? Who knows more about this? What is wrong with us? The system is upside-down!"

The Rush to the Cure

The proponents of "modernizing" FDA say that the cancer cure isn't far away—or is already here—and we are unable to see it.

"We are on the threshold of taking one of the most dreaded diseases and turning it into a curable or chronic condition," said the Journal's Pollock. "I don't think we are far off that. And I think there are a lot of barriers to that. And if one ounce of the political muscle that was put behind stem cell research was put behind rationalizing FDA policies, it would just be incredible."

Promises of the cancer cure were central to the initiation of the federal government's "war on cancer" in the early 1970s, but after a quarter century, oncopoliticians gave up on the war metaphor. In 1995, it returned with a vengeance, resurrected by the financier and prostate cancer survivor Michael Milken.

That year, Milken staged a "summit," where he presented a plan for a $20 billion-a-year campaign against the disease (The Cancer Letter, Nov. 24, 1995). His commitment to the imagery of war was so powerful that he sought to recruit the commanders of the Persian Gulf War to run the assault on cancer.

Three years later, Milken financed a march on Washington, modeled on the 1970 Earth Day. The event brought thousands of people to the Mall, but instead of producing a unified cancer agenda, it intensified the wrangling between various cancer interests. Several patient groups felt manipulated by the political and commercial interests that wanted to use the march to their advantage.

To follow up on the event, the American Cancer Society organized a group called the National Dialogue on Cancer and convinced former President George H.W. Bush and Barbara Bush to run it. The Dialogue began as something of a private club accessible only by invitation from the Bushes. It continues to meet behind closed

doors, usually in the ballrooms of Washington hotels.

Recently renamed C-CHANGE, that organization has become the political powerbase of one of its founders, the urologist Andrew von Eschenbach, who was appointed NCI director after George W. Bush was elected president. Milken isn't involved in C-CHANGE, but he and von Eschenbach have been in regular communication for years, and while their programs aren't always identical, they are concordant.

Milken says he wants to accelerate progress in medicine, and agrees with the Journal editors that the efficacy standard does harm. In an op-ed piece published in the Journal July 14, 2003, he wrote that drugs for the treatment of terminal illnesses should be subjected to a separate set of standards.

"Today, manufacturers must prove that new drugs are not only safe, but also that they work in most patients," he wrote. "That's a good standard when a drug is one of many treatment options, as it could be, say, in the case of high blood pressure.

"A different standard might be appropriate, however, for patients with untreatable terminal illnesses and no other options. Advances in genomics are expected to produce drugs that work for some patients but not others, or that are effective for some who are not at risk for side effects, even if other patients can't tolerate them."

This may be so, but skeptics point out that drug approvals have to be based on practical considerations rather than on potential great advances in genomics.

Enthusiasm has backfired on Milken on several occasions.

CaP CURE, one of his advocacy groups, provided a platform for launching the herbal treatment PC-Spes into academic oncology, but the agent was later found to be contaminated with the hormone diethylstilboestrol (DES) and the blood thinner warfarin, and was taken off the market by FDA. DES can knock down the level of prostate-specific antigen and cause regression of prostate cancer, but also causes blood clots. Warfarin counteracts the blood clots, but causes hemorrhages (The Cancer Letter, Feb. 20, 2004).

The future of one of Milken's causes—PSA screening for prostate cancer—is currently in doubt, as the medical profession is laboring to absorb the implications of the NCI-sponsored Prostate Cancer Prevention Trial, a randomized study that demonstrated that a single measurement of PSA is not an accurate method for detecting the disease.

It's possible that changes in PSA levels over time would be more useful, but randomized studies may be needed to demonstrate this.

Also, attempts to convince FDA to accept the reduction of PSA as an endpoint for development of prostate cancer drugs haven't been successful, as a group of experts convened by the agency last year found no association between PSA reduction and benefit to patients.

At times, von Eschenbach makes Milken sound like a skeptic.

The NCI director has wagered his credibility on a plan to end "suffering and death due to cancer" by the year 2015, or even sooner, if Congress is willing to add $4.2 billion to the Institute's budget over the next five years (The Cancer Letter, July 29).

Von Eschenbach hasn't attacked the efficacy standard, but he has been heard describing randomized studies the Institute funds through the clinical trials cooperative groups as trials of "Coke vs. Pepsi."

NCI Deputy Director Anna Barker, too, has been a critical of randomized trials. "[That's] not probably our best answer going forward," she said at a Milken conference April 1, 2003. "We are going to have to stratify patients, and do very specific kinds of trials."

Two years ago, the Institute floated a plan to develop agents for cancer prevention based on "surrogate endpoints," such as polyps and precancerous conditions. Such studies would have allowed drug companies to test agents in healthy people, exposing them to unpredictable consequences (The Cancer Letter, May 30, 2003).

These plans ran into opposition from the cancer prevention experts at ASCO and appear to have been placed on hold as Congress and trial lawyers sift through the data on Celebrex and Vioxx. The toxicity data on these agents emerged in randomized trials that compared them to placebo for the prevention of benign polyps (The Cancer Letter, Jan. 7).

Gottlieb: "It's a Science Problem"

Gottlieb doesn't lament the efficacy standard and doesn't frame regulatory questions in the stark terms of individual vs. the state.

Forbes marketed him as an insider, an FDA-watcher who could help you pick stocks. He was also the author of a Forbes special report titled "An Insider's Guide To Profiting From FDA Actions."

"I think our approach to cancer drug approval hasn't taken advantage of modern technologies and modern thinking about cancer," Gottlieb said in an interview before returning to FDA.

"We are stuck in an old paradigm in too many areas. We are stuck in an old statistical paradigm, even

though the tools for collecting data in the post-market and analyzing it have advanced.

"We are stuck in an old paradigm in terms of the types of endpoints we are using in clinical trials. Stuck in an old paradigm in terms of how we design clinical studies and how we enroll patients.

"That's not a Rick Pazdur problem. That's not necessarily even an FDA problem. I think it's a science problem. I think it's indicative of stagnation in development science, generally.

"It's killing patients, because you have a lot of drugs that are tested in third-line indications, not necessarily because it's the ideal place for them to be used, but from the development standpoint that's the only place where you can run clinical trials.

"It takes five years to determine whether the drug is wildly efficacious in a front-line indication, because your whole development process is geared toward non-optimal indication," he said recently, before his appointment was announced. "Think of how many breast cancer patients could have been alive many more years if Herceptin was initially approved in front-line breast cancer."

Genentech's monoclonal antibody Herceptin was approved in 1998 for the treatment of first-line metastatic breast cancer, and has since shown spectacular efficacy in the adjuvant therapy of HER2-positive breast cancer.

Breast cancer expert Sledge said the history of Herceptin illustrates the hazards of relying on expert opinion. "It's very nice of Dr. Gottlieb to say what drug was going to work, but a decade ago, the field was not there," Sledge said.

At the time Herceptin was first developed, many people felt that antibody therapy had no future in metastatic cancer of any type. In the course of clinical trials, researchers learned that the drug caused severe cardiac toxicity when combined with Adriamycin.

"That cardiac toxicity was only discovered as a result of a large phase III trial done in the front-line metastatic breast cancer setting," Sledge said. "The toxicity came as a surprise both to the company and the investigators. We are still working on the toxicity issues. It represented a huge barrier to the development of the drug. Though Herceptin is strikingly effective in the adjuvant setting, we are wrestling with the fact that 3 to 4 percent of patients develop congestive heart failure.

"So, unlike Dr. Gottlieb, we are not capable of reading the future," Sledge said. "We have to deal with the present."

Hope vs. Exploitation

After seeing the Tier 1 proposal, Erwin realized that the time had come to distance his group from the Abigail Alliance.

The Marti Nelson Foundation, Erwin's group, helps patients obtain drugs between completion of phase III trials and the FDA approval. In some cases, the group advocates for expanded access to drugs in phase II testing, but stops short of calling for broad access to drugs at that point.

Companies shouldn't be allowed to sell drugs before regulatory approval, Erwin said. Allowing drug-makers to charge for therapies after phase I testing would amount to a trip back to snake oil, he said.

"I lost my own wife to cancer, but I believe that it's important to balance the emotional reaction to personal tragedy with the logic that is important in forming public policy," said Erwin, a biotechnology company executive. "I think that's a very negative factor to induce companies to prematurely market drugs before there is adequate understanding of efficacy and safety."

Erwin said the hype surrounding emerging drugs is one of the reasons patients overestimate their usefulness.

"There has been so much over-promotion of the 'breakthroughs' in cancer research that people expect that a meaningful advance is going to add years to life, when scientifically, an advance that adds months to life is really dramatic," Erwin said. "The expectation of lay people is way off-base in terms of where we actually are in treating cancer."

In the trials of Gleevec, a drug that produced astonishing 90-plus percent response rates in chronic myelogenous leukemia, the expanded access program was opened after the company completed accrual to its phase II trial.

"I think that's the way it should be," said Brian Druker, director of the Oregon Health Sciences University's Leukemia Center and one of Gleevec's developers. "One of the real problems is that once a drug is on the market, we can't get people into clinical trials. One of the advantages with Gleevec clinical trials is that because it wasn't FDA-approved, the only way patients could get it was in a clinical trial, so we actually learned something before it hit the market."

FDA and the industry have no single set of standards for offering expanded access to promising drugs outside clinical trials. Every company invents its own program for every drug.

"The industry currently has no guidance from FDA on what expanded access programs should look

like," Stovall said. "We would like to see that guidance, and Dr. Pazdur has told us that he is eager to work with investigators, industry, and patients advocates to come up with criteria for responsible expanded access.

"No one individual in recent memory has done more to open the agency to these discussions."

For the most part, cancer patient groups are ardent supporters of evidence-based medicine. One group—the National Breast Cancer Coalition—has educated a generation of breast cancer activists to discern oncopolitical hype and deviations from rigorous trial design.

"They all have these horribly sad stories, and I wish that that were not the case," NBCC President Fran Visco said of the Abigail Alliance activists. "But my goal is to save lives, and they are undermining that goal. It's really not about them. It's about the public good.

"There is often a tension between what we want for an individual and what we want for the public good. It's difficult to deal with that tension. You hear these compelling anecdotes about an individual who has died, and yet without clinical trials, there is no reason to believe that any particular intervention would have saved this particular individual.

"There is just this hope, and it's false hope."

Bill Bro, president of the Kidney Cancer Association, sees Tier 1 as a threat to the lives of cancer patients and, potentially, a tool for their exploitation.

"I am not convinced that throwing science out the window in the name of providing some ill-defined benefit to patients is really something that serves patients," he said. "There is no question that every patient would like to have access to every drug that has efficacy in the treatment of his specific disease. But how do we get to the point where we have adequately defined efficacy if we toss out the science in the process?

"Hyping new agents as the cure is ultimately an exploitation of patients."

Gottlieb Questions ODAC's Independence

On the average, the agency rejects one drug for every four it approves.

Slam-dunk applications like Gleevec are approved by the staff, without public hearings. The advisory committee gets the problem cases, where responses are low and data questionable.

This division of labor makes ODAC into a fine venue for watching the executions of cancer drugs.

Recently, the Journal concluded that Pazdur has filled the committee with fellow industry-baiters. ODAC Chairman Silvana Martino said a description of her as an individual "notably hostile to the drug industry" didn't offend her in the least.

"I ignore those things," said Martino, a breast cancer expert at John Wayne Cancer Institute. "I think the assaults are primarily financially-based. There is an interest in promoting income to certain institutions. However, The Wall Street Journal, I suspect, cannot easily come out and say, 'That's really our intent.' And so it gets coated from a patient point of view."

Martino acknowledges her frustration with having reviewed too many therapies that claim activity in 10 to 15 percent of patients at best. "Ultimately, I am the person who walks into that room and offers patients these therapies that fail 90 percent of the time," Martino said. "I don't suspect the editors of the Journal have that responsibility."

The agency staff and the outside advisors are never completely separate, said Gottlieb, whose columns have challenged several of the committee's recent recommendations.

"[The advisors] have obviously their own authority and their own ability to reach their own conclusions, but I think they follow advice of the division," Gottlieb said. "The divisions have an impact on who gets selected to the committees, so they reflect certain philosophies.

"I don't think you can completely separate the advisory committee from FDA and absolve FDA of any role in a decision just because an advisory committee reached that decision independently."

The majority of committee members have similar qualifications. Most are academic and community oncologists.

"ODAC members are primarily people who practice medicine and who have done research all their lives, who understand the complexities of research, and who know how easily one small study can fool you," Martino said.

Members serve four-year terms. The board includes at least one biostatistician and at least one patient advocate. An industry representative is allowed to take part in discussions, but not to vote.

Doctors whose views fall outside the mainstream rarely get on the committee.

"They have an advisory committee which helps them decide, but FDA appoints the advisory committee, and they always pick advisors who are very conservative," said M.D. Anderson's Freireich. "They don't like to mess with Freireich. I've never been on their advisory committee. I've volunteered for 20 years."

Freireich has attempted to get on the M.D. Anderson's Institutional Review Board, also

unsuccessfully. "They won't put me on it, because my view is very strong that FDA should play no role in the IND process," he said.

The Industry Enigma

The office of the Abigail Alliance shows no signs of support from the pharmaceutical industry.

It's a tight space, a refurbished porch of a Cape Cod house in Arlington, Va. The walls are paneled with boards of oiled pine. Abigail's photos and plaques are on the walls, a cat named BT (short for Baby Tiger), a gift from Abigail to Frank, grooms herself on the carpet. The cat's water bowl is on the floor, and a pair of Norwegian cross-country skis is tucked discreetly in the corner.

Burroughs, a polite man of 58, moves between small desks, narrow shelves and a single chest of drawers. One desk is taken up almost completely by the computer and the telephone. Another is for recordkeeping. There, the lower right corner of the alliance's tax form—Form 990-EZ for fiscal 2003—peeks out at a visitor.

The number is in full view: year's end net assets: $32,360.27. The budget has grown a bit since, Burroughs explains. Now, it's $53,000, of which $37,000 pays his salary. Before all this started, Frank worked as a project manager, and earned twice that.

Drug companies know from the get-go that the Abigail Alliance doesn't want their money, so none is offered, Burroughs said. The entire budget comes from contributions of $20 to $100, and from fundraising events in Washington and Charlottesville.

Groups that advocate these changes don't need to take money from the industry, said Peter Lurie, deputy director of the Public Citizen Health Research Group. "If it were me acting on behalf of the pharmaceutical industry, I would keep a respectable distance and let the ideologue do my bidding," he said.

NBCC President Visco says the industry can't possibly support the Journal's anti-trials agenda or Abigail Alliance's Tier 1. "Pharmaceutical companies want to know whether their drugs work, too," she said. "If we follow the Abigail Alliance, we are going to completely undermine the clinical trials system."

The industry likes clear rules and has a healthy fear of bringing out products that do more harm that good, said Duke biostatistician and ODAC member George. "I would think pharmaceutical companies would stand to lose if things get approved that are later shown to be harmful," George said. "My experience with the pharmaceutical industry has been that they are not interested in just getting anything approved whether it works or not."

The Journal's Pollock said he detects no groundswell of big pharma support for his cause.

"The pharmaceutical companies are often very timid about FDA," he said. "They know that they have to deal with this agency, and so much depends on it that they are loath to criticize. It's conceivable that in the case of some of the larger companies, they are less concerned about the bureaucratic rules that they have to go through, because they have to deal with it.

"Hurdles always hurt the little guys more, and if we are expecting to have an explosion of new treatments to come out of little biotech companies. They are the ones that are really hurt by the current system more than J&J and Pfizer."

"FDA to Patients: Drop Dead"

On Sept. 22, 2002, in an elevator of the Park Hyatt Hotel off DuPont Circle, a scientist cast a discreet glance at the name-tag worn by a sixty-something gentleman who stood next to him.

The tag read: Robert L. Bartley, The Wall Street Journal.

Both men came to Washington for the same reason, to attend a "scientific retreat" sponsored by CaP CURE, one of Milken's organizations, which has since been renamed the Prostate Cancer Foundation.

At the same time, also in the Washington area, the British pharmaceutical company AstraZeneca was rehearsing its presentation to ODAC.

There was cross-pollination between the two meetings, and there was no way to escape discussion of the brewing drama over AstraZeneca's lung cancer drug Iressa. Bartley, a prostate cancer survivor and editor emeritus who liked to be called a "newsman," smelled one sweetheart of a story.

The agency's entire regulatory approach was about to come into question as patients who benefited dramatically—indeed, spectacularly—from the drug would stand up and tell their stories.

There was a problem. Two randomized trials of Iressa in combination with chemotherapy did worse than chemotherapy alone. (The drug appeared to actually *reduce* response rates and shorten survival by one to two weeks, though the difference wasn't statistically significant.)

However, the company also had the results of a non-randomized trial in 139 patients that showed tumor shrinkage in 10.1 percent of patients who took Iressa as a single agent, without chemotherapy.

This was less than spectacular. ODAC had to accept the company's hypothesis that for some unexplained

reason, Iressa didn't work in combination with chemo, but seemed to do better when used alone.

The agency's advisors were about to be asked to reconcile statistical data with mind-boggling testimonials.

On Sept. 24, at around 8 a.m., at the Kennedy ballroom of the Silver Spring, Md., Holiday Inn, Emory oncologist Brawley—one of ODAC's 14 members—found a Xeroxed sheet of paper on his chair. Glaring at him was the headline from that morning's Journal: "FDA To Patients: Drop Dead."

Pollock confirmed that Bartley, who died of prostate cancer in 2003, learned about the Iressa presentation while attending the CaP CURE meeting. "We were already following Iressa, but Bob did indeed seize on that opportunity for us to write about it," Pollock said.

Iressa added to the "length … of life," the Journal asserted, making a claim that went well beyond the company's application. Iressa's promise was the good news, the editorial continued. The bad news was the agency's intransigence, which would surely keep this miracle drug from the dying cancer patients.

The newspaper had no difficulty identifying the culprit: "So what's FDA's problem? Quite simply, Richard Pazdur, the FDA's cancer-drugs chief, doesn't seem to like the way companies are using fast-track drug approval process. In the case of Erbitux… Dr. Pazdur had conceded in Congressional testimony that it was a 'good drug.' But he added that the FDA wanted to 'send a message' about 'the value of doing randomized trials.'"

"When I saw the Journal editorial on my seat, I cussed a little under my breath," Brawley said. "I am from Detroit; this kind of crap doesn't work on me."

The Journal's position was anything but pro-industry, Brawley said.

"I'm pro-business, ODAC is pro-business, FDA is pro-business, Rick Pazdur is pro-business," he said. "The Journal is anti-science, pro-snake oil, and—ultimately—anti-patient."

Listening to Iressa

Before a single shred of data could be presented, nine patients who had taken Iressa showed up to tell their stories to the committee.

"We are kind of unique, because we are a happy lung-cancer story," said Rick Lesser, one of the witnesses. Next to him stood his wife Jan, a middle-aged woman, who had been diagnosed with stage IV lung cancer and came close to dying before trying Iressa.

"She is healthy," Lesser continued. "She is happy. We swim. We dive. We are spending our retirement rather dramatically. We have been diving all over the world, scuba diving…

"If Iressa works for other people like it did for us, it is the best thing that has ever happened… Jan, say something. She is not big on public speaking, but just being here is enough. Tell them how you felt and what you are doing."

Mrs. Lesser stepped up to the microphone: "Exactly what Rick said. I just—thank you very much, Iressa."

The patients who stood before ODAC weren't actually in the data. Nearly all got the drug through an expanded access program that distributed Iressa at no charge to 12,000 patients in the U.S. Not all the patients came to Silver Spring at their own expense. Some were reimbursed with AstraZeneca money distributed by a rare diseases advocacy group.

The company was asking for an "accelerated approval." To recommend approval in this category, the committee had to determine that the shrinkage of tumors was "reasonably likely to predict clinical benefit." Even when the data are strong, this question invites the agency's clinical advisors to take a guess.

The patients' stories captivated Brawley. In fact, Iressa was the only case during his four-year term when he was swayed by anecdotes. He wavered: "I started out pro, I turned con, then pro, then con. I ended up pro."

Chatting with a reporter from the Journal during the mid-morning coffee break, Brawley described Iressa as the lung cancer equivalent of tamoxifen in search of its estrogen receptor. The analogy seemed to fit. AstraZeneca had no way to identify the small percentage of lung cancer patients who were likely to respond to this drug.

Martino, who also voted for approval, has no regrets. "There were things about that drug that made me want to say, 'Ah, it doesn't work often, but it does work in some people, and when it works, it appears to be meaningful from a clinical perspective," she said.

The committee's vote –11 to 3—shook the cancer drug development world and delighted the Journal.

"Clearly, members of the general oncology community, who actually treat dying patients and from which the panel was drawn, are in no mood to quibble endlessly over data," the paper said in an editorial Sep. 26, 2002. "If the Iressa precedent stands, it will create enormous incentives for investment in new drugs."

Martino said the vote created the perception that the FDA approval standards had been, in effect,

abandoned. "Unfortunately, the experience of Iressa did place a concept in people's mind that anything would be acceptable as long as one patient got some apparent benefit," she said. "I do think that there were repercussions to that decision."

If the Journal had its way, the Iressa story would have ended right there: with tumor shrinkage recognized as a tangible benefit.

"I don't see the point in designing a trial to show the survival benefit," Pollock said. "I have never talked to an oncologist who doesn't believe that tumor shrinkage is not in and of itself a worthwhile benefit. I think that ought to be plenty to have the drug on the market, and then more studies will get done as companies seek to expand their labeling, and oncologists—who are not dumb people—will sort out which drugs are better and which are worse."

Under the agency's rules for accelerated approval, AstraZeneca was allowed to start selling Iressa, but it also took on the obligation to demonstrate that patients taking the drug were getting benefits beyond tumor shrinkage. Did progression of their disease slow down? Did they live longer? Was their quality of life better? It is, after all, possible to take the drug and have a shorter life than people who don't.

Six hours after voting for approval, Brawley concluded that he had made a mistake. "I realized that the committee—myself included—put AstraZeneca in a terrible conflict of interest," he said. "We told them that they could market that drug to all patients in second-line treatment of non-small cell lung cancer, and at the same time we told them to go search for the 10 percent of the population that they should be marketing to.

"They could make 10 times the money by delaying pinpointing the population that actually stood to benefit. To put it another way, by voting for approval, we gave AstraZeneca a license to give false hope to 90 percent of people with relapsed lung cancer."

Last December, a well-designed, randomized trial in 1,692 patients showed that Iressa was no better than placebo. Reacting to the news, both NCI and NCI Canada gave up on the agent, stopping their trials early.

The Journal's Pollock hasn't lost enthusiasm for the drug. "People with late-stage lung cancer don't just get better," he said. "We know that some people on Iressa get better. If they haven't got the trial results that show a survival benefit, everybody with common sense knows that they haven't designed the right trial yet."

It's plausible that AstraZeneca will find a way to characterize patients who stand to benefit from Iressa and run another trial in potential responders. This may resurrect the drug. It's also plausible that repeated randomized clinical trials have shown Iressa to be a bad drug with a good development plan.

Under ordinary circumstances, FDA would have left Iressa on the market. (No agent that received an accelerated approval has ever been withdrawn.) However, the Iressa situation was different, because another, similar agent, Genentech's Tarceva, was shown to improve survival, earning a regular approval.

"One would have to ask himself, 'Why would a rational physician be prescribing Iressa, with Tarceva on the market?'" Pazdur said to The Cancer Letter last month.

Stopping short of withdrawing Iressa, the agency placed it into a "limited access program." This negotiated settlement allowed the company to continue to supply the drug to the estimated 4,000 patients who are taking it, and, if a compelling hypothesis comes along, the company could restart clinical trials.

Walker wasn't impressed by this resolution.

"What an idiot!" he said of Pazdur. "He is practicing medicine by remote control from his office in Rockville, and I know oncologists who are livid over that. Who the hell does that guy think he is?"

The agency's action was unnecessary and heavy-handed, Gottlieb agreed. "The drug was unlikely to be used on a large scale by doctors, because they had an alternative when they wanted to use an oral EGFR inhibitor, Tarceva, which had better data around it, and some docs think it's a dose-loaded drug, so what was the need for action on Iressa, other than to validate a regulatory process, and is that important enough to have done?" he said in an interview.

The Journal's editorial on the Iressa action named the perpetrator in the headline: "Pazdur's Cancer Rules."

"Forgive us for getting personal, but in this case the personal is the political is the policy," read the July 6 editorial. "FDA oncology drugs chief Richard Pazdur is the most important person in the U.S. government when it comes to cancer drugs, and he has never made a secret that he dislikes the accelerated approval process under which Iressa got the green light. Nor has he been shy about suggesting that the agency was railroaded in this drug's case."

In this explosion of indignation, the editors omitted one little detail: Iressa's failure to beat the sugar pill.

In an email blast that morning, Burroughs forwarded the Journal piece to his friends and contacts. "Another editorial from Rob Pollock," he wrote. "As usual, we worked with him on this one."

A Notch-Signaling Pathway Inhibitor in Patients with T-cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

An investigational study for children, adolescents and adults with relapsed and refractory T-cell acute lymphoblastic leukemia/lymphoma is now accruing patients at various centers around the country.

This study's goal is to evaluate the safety and tolerability of a Notch inhibitor as a rational molecular therapeutic target in T-ALL, potentially uncovering a novel treatment for these cancer patients.

Eligibility criteria and treatment schema for the study include:

Notch-Signaling Pathway Inhibitor in Patients with T-ALL	
Eligibility Criteria	Patient must be = 12 months with a diagnosis of T-cell acute lymphoblastic leukemia/lymphoma AND must also have: • Relapsed T-ALL • T-ALL refractory to standard therapy • Not be a candidate for myelosuppressive chemotherapy due to age or comorbid disease ECOG performance status =2 for patients >16 years of age OR Lanksy performance level >50 for patients 12 months to =16 years of age Fully recovered from any chemotherapy and >2 weeks from radiotherapy, immunotherapy, or systemic steroid therapy with the exception of hydroxyurea or intrathecal therapy Patient must be >2 months following bone marrow or peripheral blood stem cell transplantation No treatment with any investigational therapy during the preceding 30 days No active or uncontrolled infection
Treatment Plan	Open label and non-randomized, this study is conducted in two parts. Part I is an accelerated dose escalation to determine the maximum tolerated dose (MTD), and Part II is a cohort expansion at or below the MTD. MK-0752 will be administered orally. Plasma concentrations will be measured at defined time intervals.

For information regarding centers currently open for enrollment, please contact 1-888-577-8839.

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