Into the Light:
The story of one drug and America's drug approval process.

By Lane Williams

It took Photofrin, a drug useful in treating some forms of cancer, more than 20 years to reach the market following its discovery. Why did it take so long?
While it is tragic that many people have died from adverse drug reactions, that thousands have died who might have benefited from delayed drugs is an equal human tragedy.

One of the great miracles of the nuclear age is that for the thousands killed by atomic radiation, millions have beaten cancer through its benefits.

Doctors' task is to give radiation in high enough doses to destroy tumors without damage to patients. Unfortunately, when low levels of oxygen exist in a cancer cell, it won't respond well to radiation, and the radiation dosages for cancer can become harmful. One of the great research quests is to make radiation therapy more effective.

In 1972, Thomas Dougherty, Ph.D., was working on this problem at Roswell Park Memorial Institute in Buffalo, New York. Dougherty looked for a drug to produce oxygen so cancer cells would be more susceptible to the effects of radiation.

One test he ran was vital staining, which helps scientists tell what cells survive a drug treatment — an excellent way to determine the effectiveness or danger of a proposed therapy. Scientists inject cells with the test substance and, later add fluorescein diacetate, a kind of light activator, and then let the cells sit for a few hours. The surviving cells will glow green.

Dougherty was running this test when a simple suggestion changed the course of his career. A quarter century later, Dougherty cannot remember the name of the technician nor her exact words, but the gist remains clear. She said, “Don’t leave the cells out in the light or they will die.”

This process causes cells to emit light, but can also kill them. Why not use light to kill cancer? Dougherty thought. Why not develop an entirely new therapy?

For 25 years now, Dougherty has pursued practical applications of this idea, now called photodynamic (or sometimes photosensitization) therapy. If nothing else, the story of this therapy shows the creative, exciting process by which new miracles come to market, marking drugs up there with the great human achievements like the Apollo moon shots or Voyager’s pictures of black hurricanes on Neptune.

Unfortunately, this story also shows how the complexities of drug approval in the United States nearly killed a promising idea. This drug is an excellent case study of how bureaucracy, namely the Food & Drug Administration, can block progress, how the complexities of the market can feed expense, and how the increasing complications of clinical trials can increase the cost of new drugs, hindering their development and, ultimately, costing people their lives.

Many talk of the dangers of delay during the FDA’s approval process. What seems to be missing in much of the debate over reform, however, is the time it takes to complete clinical testing of a new drug before submission for approval ever occurs. The length and complexity of clinical trials have grown for three decades now and show little signs of letting up.

Consider these statistics: For every 6,000 to 10,000 chemicals tested in laboratories, only one becomes a new drug. For each new drug that enters the market about three promising chemicals fail to meet the rigorous of clinical trials and fall into the chemical junk bin.

Why care? Delay can cost lives. You may lose your life by ingesting a
poisonous drug, true, but you also might die through delays of a drug that might have helped you. It is impossible to say precisely how many die from delay, but pretend that only six in 100 of lung cancer patients who might have benefited from Dougherty’s work had done so since 1980, then some 60,000 lives might have been saved or improved — more lives than the country lost in Vietnam. Instead, only those fortunate enough to be a part of clinical trials saw any benefit.

Indeed, you can find other examples of the costs of delay. The Hudson Institute, a think tank in Indianapolis, estimates that as many as 8,000 serious complications from heart valve transplant surgery a year in the United States might have been prevented because a superior device has been kept off the market.

In my research, I found I have a personal stake in this story. I’ll disclose it. My father suffered recurring, life-threatening ulcers that bled about the time scientists were developing life-saving Tagamet and its descendants. I realized, first hand, how the process of drug trials affects individuals needing life-saving treatment.

At first, it was easy for me to simply blame the FDA for all the problems in drug development, but the issues are much more complex. I came to the issue of serious FDA reform from the perspective of running a trade magazine for a nutritional supplement company. The FDA is a hassle and a byword there. The agency rarely seemed to respond with an open mind to the beautiful power of herbal supplements nor did it show much respect for the growing body of science behind them. Though I did not share many of my colleagues’ more extreme views of conspiracy, I had some disdain for the agency.

What I found at FDA, however, were earnest, intelligent people who have been cut under a generalized and less research. The FDA is responsible for products that make up one-fourth of the U.S. economy with a relatively small budget, as the federal government goes. It is trapped between extremes but, unfortunately, speckled by a few cases of what seem to be egregious bureaucracy.

Some of this story fits here. Dougherty’s work ran up against a powerful agency in frustrating ways, but his story involves more. Hence, it is a great case study to illustrate the difficult details of clinical trials and drug development in America today.

The origins of photodynamic therapy show up in Hindu writings in 1400 B.C. Doctors used the seed of the bavachee plant and exposure to natural sunlight to treat vitiligo, a disease where people of color find splotches of skin becoming lighter. (This is the disease entertainer Michael Jackson says he suffers.) Records from the medieval Middle East talk about a similar therapy. In the later part of the 19th Century, German scientists accidentally found ways to use this photodynamic principle in treating certain skin conditions. But it fell to Thomas Dougherty in 1972 to bring this therapy to cancer treatment.

After hearing about leaving a petridish with fluorescein out in the sunlight, Dougherty immediately tested his new idea. The combination of fluorescein and light killed cells, but problems followed when he tried to kill cancer. Fluorescein doesn’t stay around in cells very long, and some light won’t penetrate tissues very far.

Sometime when you’re in a dark room, ask friends to stick flashlights in their mouths. You’ll notice red light coming through their cheeks. The soft tissue absorbs it but the red light. Fluorescein is activated by green light, and he needed something to work growth slowed in animals, but the tumors survived. Still, he was onto something. The chase was on.

Dougherty read about tests at the Mayo Clinic where scientists used red light and a substance called hematoporphyrin derivative to detect tumors. (Dougherty credits Richard Lipson with being the first to attempt briefly to use photodynamic therapy in cancer in 1957.)

Dougherty synthesized hematoporphyrin derivative from animal blood and began experiments. He applied for a grant. Two years had passed.

Unfortunately, those who give grant money couldn’t figure out how Dougherty would get light into cancer cells. His request was denied. He had to find another way to get money.

The U.S. system of drug approval is a complicated multi-billion-dollar-a-year industry. In 1995, for example, the FDA approved 62 drugs. Of those, 28 were new chemical entities, products containing an active substance never before placed on the U.S. market. Estimates vary, but it now costs some $350 million to get a new drug to market after 12 years of exacting research. For perspective, $350 million equals one-third of the entire budget of the FDA for one year. (FDA Associate Commissioner Randy Wykoff takes issue with the drug industry’s estimates of $350 million. He said business includes the cost of all failed drugs in its calculations, thereby skewing the amount one new drug costs.)

The first step in development is when scientists find a substance that seems to work in the test tube. These substances may come from plants or, increasingly, may come from sophisticated computer programs that diagram molecules and simulate chemical effects.

Next, technicians test the substance on animals to look for toxic effects. In
Lane Williams

Drug Approval

takes to kill it. With complex mathematics, they can determine how much might be safe for a human.

Next, scientists ask the FDA for an Investigational New Drug application, an IND. When approved, testing in humans begins. The first step of human testing is toxicity testing or Phase I. Doctors give gradually increasing doses to 20 to 80 test subjects. Scientists determine what they consider a minimum tolerable dosage.

In Phase II, scientists look for effectiveness. Using about 200 patients, doctors give “safe” doses and see how well it works. A good cancer trial might look to see if a tumor decreases in size. Doctors look for side effects.

The last portion is Phase III. Scientists use large numbers of patients, maybe 3,000 or more, to monitor the effectiveness of a particular drug and look for longer-term side effects. These trials are usually controlled by placebo — using a group of patients suffering the same diseases that receive what amounts to a sugar pill.

Researchers next analyze the data. (A new phase is emerging in trials called Phase IV to study longer-term effects after a drug reaches the market.) Next, companies submit a New Drug Application — an NDA — to the FDA. The FDA must decide whether the tests were adequate and whether benefits outweigh risks. Only about one in four drugs tested in humans will ever make it to a pharmacist’s shelf.

Approval times have dropped dramatically in recent years. This is significant in the light of criticism of the agency. Between 1990 and 1992, the average amount of review time for a new chemical entity was 2.6 years, according to the Center for Drug Development at Tufts University. In 1993, the average was only 1.3 years, the FDA says.

The rub comes elsewhere. Overall development times have jumped. According to Tufts’ Center, in 1963, six years passed from the time a substance emerged in a lab until it was ready for the market. By 1993, that figure was nearly 14 years, though down slightly from 1990.

In 1995, Tufts’ Kenneth Kaitin, Ph.D., also found only 33 percent of recently approved drugs were approved first in the United States, though 86 percent of recently approved drugs began clinical trials here. Of drugs approved between 1990 and 1994, one in five were available elsewhere for more than six years and one in 10 for more than a decade.

Other facts from Tufts’ studies:

- In 1995, it took about 8.5 years from the time a drug is first tested in humans to the time of FDA approval, and three-fourths of that time was in clinical trials.
- Research trials increased 140 percent between 1963 and 1993, and the time from initial synthesis to approval jumped by 156 percent.
- Of particular note, in the 1960s, clinical trials took an average of 2.5 years. Today, it takes more than six.
- The issue of pharmaceutical reform is locked here in the clinical trials and in development times. Thomas Dougherty became a case in point.

For him to even get to clinical trials on his light therapy, Dougherty needed money. He applied for a second grant. This time, he received money.

For two years, Dougherty tested hematoporphyrin derivative in animals, looking for toxic effects. In 1976, human testing began on 30 women.

The women entering the trials had advanced breast cancer, which had spread to the skin. First, doctors injected the drug into the patient and then exposed the tumors to red light from a lamp. The tumors shriveled and died. Unfortunately, so did most of the women in the tests.

Photodynamic therapy with hematoporphyrin derivative can have some unpleasant side effects. Most notable among them was that for four to six weeks following treatment, patients are subject to intense sunburn. For a dying person to give up hours enjoying the sun is asking a great deal. “It’s incredible,” Dougherty says of these patients. “When you talk to people like this, you wonder if you would be as generous.”

For two years, Dougherty and his colleagues riddled with treatment. In 1978, as he remembers it, Dougherty delivered a paper on his exciting results at a conference in Washington. FDA representatives attended.

No one had consulted the FDA nor filed any applications for an Investigational New Drug. Their reasoning was simple. Roswell was self-contained. Pharmaceuticals were developed and mixed on site. Patients and research were at the facility. The work was local. The FDA has jurisdiction only over interstate commerce.

Soon, a phone call came from an agency official asking why no application had been filed. Dougherty outlined his clear reasons. “The gentleman on the phone asked, ‘Where did you get the bottles that you put the drug in? I didn’t know, but I got the message.’” Somehow, the FDA would find an interstate connection to be in charge of the research. It had been six years since Dougherty first tested cancer cells with fluorescein. “They told us to stop the trial.” Again, it seemed this promising idea might well face death penalty for reasons outside of its possible benefits to patients.

The origins of modern drug regulation take us back to the days of Upton Sinclair and his most famous book, The Jungle. His serialized novel was not successful in effecting the Socialist revolution he seemed to envision, but its famous depictions of life in the slaughterhouses of Chicago led Congress to establish the Pure Food and Drugs Act of 1906, which established the agency that became today’s FDA.

Until 1937 and a sulfanilamide tragedy, no one required companies
Drug Approval

selling pharmaceuticals to test for safety or effectiveness. On the theory that many people preferred to drink medication, one corporation decided to make a sulfanilamide elixir — something mixed with alcohol. Unfortunately, sulfanilamide, a precursor to penicillin, didn’t mix well with alcohol, so a chemist used diethylene glycol. Diethylene glycol is the basis of antifreeze and has the same effect on people that it does on house pets enjoying tasty drippings from abandoned vehicles. Investigators figured more than 100 people may have died. The grief-stricken chemist committed suicide. In 1938, Congress passed a law requiring all drugs to undergo safety tests.

The next big change came in 1962 with thalidomide. Thalidomide — a word of terror — came onto the market in Germany in 1957. Europeans used the medication as a sedative and its German developer, Chemie Gruenthal, which brought the world the antibiotic streptomycin, sold more than 16 million Deutchmarks worth in 1961 alone. It hid much of the truth about thalidomide, however, which caused nerve damage in adults and horrible, often fatal, birth defects in children.

In the United States, more than 2 million doses went to people as tests, but the FDA never approved thalidomide. Only 18 documented American babies had deformities from thalidomide. Dr. Francis Kelsey of the FDA received credit for preventing the tragedies in this country. For her work, President John F. Kennedy took the rare step of awarding her the President’s Award for Distinguished Service, the highest decoration for civilian service.

Some have argued, such as author Walter Ross, that the award, a first for the agency, had a negative impact. Kelsey’s work keeping thalidomide off the market, the reasoning goes, came not so much from an expert opinion but from indecision. President Kennedy’s medal, therefore, reinforced an ethic that celebrated four of the things bureaucracies already do best... deliberate... vacillate... contemplate... and... hesitate.

Senator Estes Kefauver led the fight for new legislation that would require that all new drugs entering the market to be shown as effective, not just safe. The results were striking after passage: In the decade leading up to the thalidomide tragedy, an average of 49 new drugs entered the U.S. market each year. In the decade after, the yearly average was only 17.

The New York Times said in December 1995 that thalidomide is enjoying something of a renaissance. Many patients suffering from such intractable problems as AIDS, tuberculosis and macular degeneration, a leading cause of blindness, report relief of suffering.

Thalidomide shows the irony of modern drugs and the pressures today’s FDA faces. With chronic problems like AIDS, what is the ethical problem of giving this or any drug to people suffering from a terminal illness? For more than a decade now, researchers and activists have debated this issue. This resulted in the exciting decision to approve saquinavir, a new kind of AIDS drug, on December 7. It took only 97 days for the FDA to grant approval.

This example goes well with the FDA’s argument that it has cut drug approval times in the last five years.

Not everyone agrees. “The agency is in the process of destroying itself and, frankly, it has to be saved,” says Peter Hutt, a Washington attorney who served as general counsel for the FDA in the 1970s. He teaches a food and drug course at Harvard, and is one of the agency’s most vocal critics. Hutt says the FDA has done three things to make its statistics look better. One, the agency counts time in new ways, stopping its clock each time it asks for more information, he says. Second, it asks some companies not to file and, third, it has developed a procedure called “refused to file.” This means that the agency won’t begin counting review time until a second petition comes, say, six months later.

How long is it actually taking? “I just don’t know whether anybody is keeping the real statistics,” he says. “If you start cooking the books the way they have, then you can make it look” better than it is.

Another effect, he explains, is the time required to approve a drug may seem to decrease, while the time required to study it increases.

Ken Kuttin of Tufts University says most experts see three major reasons that it is taking longer for drugs to reach the market. One reason, he says, is the increasing complexity of diseases science is trying to tackle. A second reason is the increasingly detailed marketing research done by companies before they file an NDA. The third reason is FDA seems to have more regulatory requirements.

This third reason is an old argument.

One of the best examples of this comes from a 1968 photograph of Parke-Davis employees looking up at a photographer. Or a table next to them are five drug applications submitted to the FDA over 30 years. On the left sits a drug application filed near the end of the Depression. The application needed only one thin folder and stretched a paltry 27 pages. The drug? Adrenalin. On the right, a smiling, middle-aged woman with a ‘60s’ hairdo and a conservative dress holds a plainly lettered sign counting the pages of an application to her right towering three times her height. It was the application for a drug called Ketalar with 72,200 pages of data.

Today, such an application would be small. At an industry-sponsored conference in Philadelphia last year, Hoechst-Roussel Pharmaceutical’s Paul Conway showed statistics about the average size of New Drug Applications. As of 1992, the average length was more than 90,000 pages.

Indeed, the amount of data required for approval has been itself a kind of
malignancy. Between 1977 and 1980, the average application had some 38,000 pages. Between 1981 and 1984, the average application had some 45,000 pages. In the next three years, the average application jumped to about 56,000 pages. Between 1989 and 1992, the application again grew to 90,650 pages—a 38 percent jump.

Why such a significant jump in the amount of data required? There aren’t agreed-upon answers, but it is worth noting that in 1987, before the 38 percent jump, the FDA completed a rewrite of regulations of how to file a New Drug Application.

The FDA of 1976 could have been much more prickly with Roswell Park and Thomas Dougherty than it was. Although it ordered him to stop testing photodynamic therapy in humans, it did so only partially. On a case-by-case basis, he was allowed to continue his work. The FDA, however, required an Investigational New Drug application which required redoing some research, killing additional laboratory animals and finding $500,000, more than 14 times his grant.

Again things seemed doomed, but Dougherty found a way to use his old data for the application, which the agency accepted. “I can tell you that would never happen again. The FDA has become much more restrictive.”

Strong results began to come. One woman saw a complete recovery. The patients entering tests to this point were not in the early stages of the disease, so treatments may not always have the full benefit they would in effecting a cure for a patient earlier in the dramatic course of malignancy.

The scientists wanted to prove this might be a viable cure, so Dougherty asked veterinarian Richard Thoma to apply this treatment to animals with cancer. By now, photodynamic therapy had advanced to using lasers and fiber optics to deliver red light directly to tumors blocking airways or the esophagus. Thoma took a laser to his clinic and used a small needle to get the light fiber into an animal. Cancer in animals is considered cured after two years (as opposed to five in humans) and, by that criterion, 65 of 100 animals were cured.

About 30 research centers around the world began to work on this new therapy, each demanding samples of hematoporphyrin derivative. The pharmacy at Roswell Park couldn’t keep up. What is more, Dougherty found that shipping experimental drugs around the world was another violation of FDA regulations.

So, Dougherty decided it was time to get a drug company involved. He worked with one of the giants, Ciba-Geigy. Dougherty hoped Ciba would produce the drug to continue the clinical trials and, ultimately, to get it to market. For Ciba-Geigy needed something to patent. Hematoporphyrin derivative was widely discussed in the literature, so no patent was possible.

Eight years into his quest, Dougherty hit a business snag.

Ciba dropped the project and Dougherty had to find a new way to cross the latest hurdle.

The issue of patents is one of those factors influencing companies. Some believe that patent issues may decrease the amount of research companies will spend on developing new drugs because the amount of time a company can have exclusive market rights to a drug is decreasing.

This is just one business hurdle. The popular rise of generic drugs marks a threat to the profit-incentives of innovators.

Another threat is liability. According to The Progress & Freedom Foundation, between 1976 and 1989 the pharmaceutical industry carried a total burden of liability cases about half the rest of the country’s manufacturing businesses combined.

The point? According to Joe DiMasi, an economist at Tufts, between 1985 and 1989 29 of 100 new drugs in testing he sampled dropped from research simply because of economic concerns. Also, these market reasons have grown more significant since the 1960s.

On the other hand, watchdogs of the pharmaceutical industry, such as the group Public Citizen can attack marketing and business work. Much of the new pharmaceutical innovation in this country is not for new, novel therapies, but for pills competing for the never-ending money supplies found in common disease. The recent splashes of Tagamet, Pepcid, Axid and Zantac into the over-the-counter antacid pool are a case in point.
Drug Approval

What other issues are affecting drug development? Why, for example, are clinical trials getting more complicated and time-consuming?

Not only is the number of pages per New Drug Application increasing, but the number of patients in trials and the number of trials per new drug keeps jumping. Hoechst-Roussel’s Conway said at the Philadelphia conference:

- In 1977 to 1980, the average number of clinical trials per New Drug Application was 30. By 1989-92, the figure had doubled.
- The average number of patients in each trial went from 1,576 to 3,567.

On one level, more complicated diseases are responsible for the growth, as Tufts’ Kaitin says, but more is at work here. It only seems natural that as science finds ways to test for new effects, ever-increasing numbers of tests become standard parts of the drug-testing process. Hence, each New Drug Application can require more blood tests causing delay. On the other hand, if you can learn important new things through a new, relatively simple test, is it entirely ethical to neglect those tests?

Remember the Sorcerer’s Apprentice? The tools of clinical trials take on lives of their own. The more science knows, the more complex and expensive a test can be.

This would be problem enough if scientific testing were a perfect instrument. Unfortunately, each scientific project has some level where details can fall apart. One man who understands this is Donn Young, a biological statistician who supervises the design of 20 to 25 human studies at the James Cancer Hospital at Ohio State University, among the largest such centers in the country.

One example of the difficulty of designing a potential clinical trial is prostate cancer. Young says it can take a decade or even more for this lethal cancer to complete its work. So a detailed trial could take decades involving thousands of men to see if a cancer treatment cured patients. This is essentially impossible. The trick becomes looking for other “end points” that show a cancer would likely be cured. An end point might be a smaller tumor or it might be a decrease in certain chemical agents in the blood stream.

Even if a study were designed perfectly, what about the logistics and implementation? Someone has to take care of all that. I met Karen Hale, a pharmacy administrator at Ohio State, in her office at the end of a long, orange-painted corridor near warnings of biological and radiation hazard and near emergency instructions. Hale took me through the logistics of one clinical trial.

It is a Phase II test for sepsis, an acute blood infection. Sepsis strikes suddenly through bacterial mechanisms not entirely understood. Its toxic effects, when not caught early enough, are often so far advanced that antibiotics can’t prevent death. Bacteria can be defeated in many ways. One is to kill them outright with antibiotics. Another is to counter the effects of endotoxins, the chemical tools bacteria use to do their grim work. This possible medication is to battle endotoxins.

Consider some of the headaches involved:

- This medication must go to numerous research centers at the same time.
- Each center has an Institutional Review Board that sit as a watchdog to protect patients from poor ethics. Any institutional board can create trouble for a company pushing a new medication. These boards, and a federal agency that oversees them, began with an act of Congress, when America learned of Black men in Alabama earlier this century who suffered with syphilis as a part of research, though therapies were available.
- Patient records must be kept. At Ohio State, these go in a locked room near Hale’s office.

Each clinical trial has its own set of logistical headaches. In the sepsis trial, two unique logistical issues emerged:

- The bottled IV test drug is clear, but the placebo is a straw-like yellow.
- How do you hide the placebo from the nurses administering a dosage?

The FDA expressed concern that small particles might coalesce within the drug. This is a major danger to patients receiving an IV.

To combat the first problem, the drug manufacturer provided orange plastic sleeves for each dose of the drug. This covers the clear bottle so no one but the pharmacists can see the color of each bottle’s contents. Each dose requires this sleeve.

To find particles, the drug maker provided a small desk lamp, polarized sunglasses and a small black-and-white metallic plate. With back lighting from the lamp, a pharmacist looks through the glasses at the bottle toward the metal plate behind.

As I tried to mimic what the pharmacy does with each dose, I twirled one bottle of medicine in my hand. Looking through sunglasses, I saw air bubbles spin cleanly upward. Any dark particles in the clear bottle would have spun downward, easily visible against the white of the metal plate behind. I saw no particles. This one was OK to administer.

These logistical issues were simple, undramatic events in a drug trial, but each little headache . . . like orange sleeves to hide the color of a drug . . . and polarized sunglasses . . . and the logistics of providing black-and-white boards to hospitals around the country . . . and patient follow-up . . . and
detailed records in locked rooms ... all showed me why this process is so daunting and expensive.

Clinical trial expense was a big headache for a small company in Decatur, Illinois. Inventive Products, Inc., is the brainchild of 66-year-old Earl Wright. (Wright invented a blood-serum filter for laboratories, corn silk make-up, and a non-aerosol cleaning pump for the space shuttle.) His simple Sensor Pad looks much like a deflated balloon, about eight inches wide, sealed all around with greasy lubrication inside. Approval took 10 years and cost more than $2 million.

Sensor Pad started as a concept looking for a market: If you can reduce friction, the sense of touch improves. When you set the pad against something, the bottom sheet stays still, and the top sheet slides on the lubricant, improving the sense of touch. Innovative Products says Wright considered using Sensor Pad to help blind people read Braille more easily, but the Wrights settled on the breast self-examination market.

Many doctors believe regular breast exams help in early detection of cancer. The Sensor Pad's role would make exams more convenient. Grant Wright, Earl's son, says doctors often advise women to use soap and water while doing the exams — as a way to reduce friction.

The Sensor Pad ran up against the FDA, however. When Grant submitted the device for approval, the agency said no other device to find breast lumps existed in the U.S. market. This whooppee-cushion-like pad was deemed entirely new, so bureaucrats classified Sensor Pad with things like mechanical lungs and dialysis machines.

The FDA wanted extensive testing to see if the pad helped women find lumps in their breasts. This is difficult. A complete test could take tens of thousands of healthy women or many years to complete. Inventive Products did some tests, but nothing exactly as FDA seemed to want.

The company had its success stories. In 1990, a woman named Mary Gorman used a Sensor Pad only four months after a clear mammogram and found a lump. Gorman went to her doctor with the news. The lump was cancerous, and the doctor removed it, one of the smallest malignancies she had ever cut out. Six years later, Nancy Gorman is free of the disease. She told Congress Sensor Pad "may have saved my life."

By 1995, Sensor Pad's patent was running out, and $2 million were gone. Congress invited Earl Wright to testify, and he told the House Commerce Committee he was ready to give up.

After the hearing, it took only four months for FDA to find a loophole and approve Sensor Pad.

Grant Wright, 35, shares his father's entrepreneurial drive, but the battle has taken its toll. Wright is not one to bad mouth the FDA nor the role of clinical testing, but as a businessman, "I do not want to touch another medical product, and that's a helluva thing to say at my age," he says. "I shouldn't feel that way."

Another example of the FDA's power came in 1989 when the agency denied an application of Minneapolis-based Medical Incorporated to sell its Omnicarbon heart valve in the United States, a prohibition that remains to this day. The FDA was concerned with the ceramic material it came from.

However, approval in Europe came in 1987, where more than 25,000 have received the valve.

More than 400,000 Americans have mechanical heart valves, and about 16,000 each year have a complication involving internal bleeding, which can lead to stroke. Results in the 25,000 implants in Europe show the Omnicarbon heart valve has about half the failure rate compared of other valves, reports The Hudson Institute.

Half the problems of 16,000 annual complications saves 8,000 people trouble in a year. That's conceivably more than 50,000 people benefiting in the seven years since the FDA denied the Medical Incorporated's request.

Shelly Johnson, the vice president of medical affairs, says the application to the FDA is not finished, technically. Medical Incorporated has provided some information, and the FDA has looked at it, "but I would not classify what's going on as real active. It's not a dead issue, but it's not as though we are beating each other's door down." She keeps a file of news stories about bureaucratic delays with FDA, but you can almost hear her shake her head in disbelief at her own story. "I never would have believed this unless I was right in it."

After Ciba-Geigy decided it did not want to pursue Thomas Dougherty's research on photodynamic therapy, he didn't give up. Since hematoporphyrin derivative could no be patented, he found the ingredient, porphimer sodium, or what has come to be called Photofrin.

Dougherty went for his own patent. Working with veterinarian Richard Thoma and Ker Weishaupt, Dougherty formed Oncology Research and Development. They filed for a patent and began to produce Photofrin themselves out of a former liquor store.

The cost of bringing the drug to market was well beyond the resources of Roswell Park, but the trio pressed forward and constructed a small manufacturing facility. For two years, ORD scrambled for funding. Then, in 1983, Dougherty delivered a scientific paper. Representatives of Johnson & Johnson, the personal products giant, attended. Photofrin looked like a drug to take J & J into the lucrative field of cancer pharmaceuticals. The representatives approached Dougherty and, after a year of negotiation, J & J acquired the rights. This was more than a decade after Dougherty's quest.
Drug Approval

for photodynamic cancer therapy began.

Dougherty says the first six attempts at manufacturing Photofrin went poorly for the giant company. Other delays ensued. Johnson & Johnson wanted a new Investigational Drug Application under its name, and this required a new battery of animal studies and lab tests. When human testing began for Johnson & Johnson, doctors needed patients not responding to standard therapies. This took time. After three years of investment and nothing to show for it, Johnson & Johnson began to rethink its decision and prepared to cut its losses.

The lights seemed to be going out on Photofrin again. It would need an unlikely hero to save it.

You can find references to light in many religions. It leads to a holier life, to enlightened understanding or to deep truth. The Bible begins with God saying, "Let there be light." Ancient Egyptians portrayed light with their sun god. Light, indeed, is life. Ironically, it is also death.

Light breaks itself into numerous unique wavelengths our eyes see as the finite colors of the rainbow. Isaac Newton named only seven colors of the spectrum because he liked the analogy with the seven notes of the musical scale. Each wavelength of light can affect electrons in our cells, exciting them to higher levels of energy. At higher energy, new chemical reactions occur.

With photodynamic therapy, certain drugs gather laser light, which is then transferred to oxygen in tissue. The oxygen becomes singlet oxygen, a potent, short-lived molecule. This agent kills cells by ripping apart important chemical bonds.

When it became clear that Johnson & Johnson was about to kill its Photofrin project, a Columbus, Ohio, doctor, James McCaughan, took matters into his own hands. McCaughan used Photofrin in lung and esophageal cancer.

Cancer of the esophagus is difficult to attack with a surgeon’s knife and has the horrifying side effect of cutting a patient’s access to food as the tumor inexorably progresses. Photodynamic therapy gives hope. Though the cancer may still kill, the 12,000 Americans who are diagnosed with this disease each year have the potential of great relief and possible cure, if detected early.

McCaughan bought stock in Johnson & Johnson and promised to take patients with him to a shareholders’ meeting to say that the end of the Photofrin project would sign the patients’ death warrants, the Columbus Dispatch wrote. Johnson & Johnson agreed to sell the rights to the product, rather than killing it outright.

A small company in Vancouver, British Columbia, QLT Phototherapeutics, bought the rights. QLT worked with Lederle Pharmaceuticals, which took out a small equity in QLT. Together, they pushed the drug into clinical trials anew.

(Though not every drug on the market gets passed around like Photofrin did, such issues are real in the marketplace. Indeed, many pass from federally funded research to private hands, Ohio State’s Young says.)

Dr. Julia Levy, an immunologist, founded QLT in 1981 with a University of British Columbia colleague. Her interest in these kind of drugs began when her children ran through a field of cow parsley, a light sensitizer, and became intensely sunburned.

Levy's work led to Photofrin. Lederle and QLT’s new trials meant new delays associated with a new set of patients to study. By 1992, things were again progressing well. Still, Photofrin needed to survive one more death warrant. Lederle was a division of the giant American Cyanamid, which was becoming a victim of hostile takeover. Lederle's scientists were dispersing to other jobs. Photofrin was poised to disappear yet again.

Solutions to the problems of lengthening drug trials are illusive. The Republican Congress is making an attempt. One bill in the House, H.R. 3199, has received the most attention. It would have allowed small companies to act as reviewers of drug applications. The FDA would oversee these companies, which could not be involved in medical research themselves. The general principle is: competition among these firms would encourage the fastest, best approach toward speedy drug approval.

This has little to do with clinical trials, however, which are completed before an application is ever reviewed. What would the law do for clinical trials?

First, it would allow a company to begin trials 21 days after submitting an Investigational Drug Application unless the FDA specifically forbade them. The bill also tries to explain exactly what is required, so the agency can’t keep arbitrarily asking for more. Another provision would allow certain research centers to set up their own clinical trials in limited circumstances. The bill would also allow companies to go to the agency and request a meeting within 30 days to discuss a clinical trial. Reviewers would be forced to follow guidelines of the agency division responsible for each new drug for consistency.

The bill was never voted on in the 104th Congress, and similar provisions have yet to pass the 105th.

Why not just eliminate effectiveness testing in the first place? Didn’t the country do well enough without them until the thalidomide scare? Didn’t the country mostly get through the thalidomide scare, in fact, with relatively few injuries compared to Europe?

William Wardell, a long-time proponent of less restrictive drug approval says such a scheme isn’t workable. The reason, he argues, is not perfectly
safe drug exists. Patients and doctors must have a sense of what a drug might do to make any reasonable judgments.

For the FDA’s part, it is trying to find new “endpoints” to show a disease is improving, and to test for those. The agency also says it is working with companies earlier in the process.

Dr. Randy Wykoff, an FDA associate commissioner, speaks passionately and proudly about how important the FDA can be. “We’re not talking about a black-and-white science. We’re not callous bureaucrats. We’re not out of touch. The reason we do it is because we believe the FDA brings tremendous value to the process. I couldn’t practice just on the basis of anecdotal experience.”

Wykoff says the agency has worked to ensure individual reviewers must answer to supervisors, so arbitrary changes will be less likely. He said the pharmaceutical business often asks for more data in clinical trials as well, so clinical delay isn’t just the FDA’s concern.

He says science is quickly expanding to find better ways of measuring the development of disease. This may decrease the time it takes to do trials in some cases. Wykoff also says the agency is working to provide test drugs to patients where it would be their best hope.

Wykoff compares the FDA and the drug development process to a pendulum. It swings trying to find a line of perfect balance between safety and access. Today, people seem to want more access, but, he says, “There will never be a time in which everyone will agree that we have drawn the line in the right place.”

Some observers say since Republicans came to power, the FDA has transformed itself. Joel Noble, president of ECRI, a 210-person organization that publishes a Consumer-Report-like medical device evaluation program, is one. One year ago, the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate. Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.

It is people in a democracy who ultimately decide where the pendulum should stop. In his book The Life/Death Ratio, Walter Ross describes an unusual 1970 experiment that underscored how much people might be willing to tolerate.

Louis Lasagna, now the director of the Center for the Study of Drug Development, put an unnamed headache remedy in front of his subjects. He told each of the dangers of the drug, which can cause internal bleeding, anemia and, in rare cases, death from only one tablet.

Many expressed relief they didn’t have such a dangerous substance at home. The drug was aspirin. Scientist Alfred Burger wrote in 1965 that the FDA wouldn’t have approved aspirin in his day. Would it have today? No one really knows.

Peter Hutt, the agency critic, believes that much of the drug approval process is misunderstood. Toxicology testing is about finding what amount of a drug causes toxic reactions. It has changed so much that not only has the horse changed its colors, but it is hard to still recognize it as a horse any longer, he says.
Drug Approval

ment. One suggestion has become his life's work.

Whether Photofrin will succeed on the market remains to be seen. Levy says QLT is working to launch the drug, but careful marketing in an era of managed care is important. Many drugs don't make back their investment. Levy says, "I used to think bench science was tough."

Photofrin's legacy, though, isn't about market share. It is about lives saved. Ten years ago, Betty Pifer was diagnosed with lung cancer. She went through a standard course of surgery. For four years, she was relatively cancer free, but in a 1990 check-up her specialist found an inoperable tumor on one bronchial tube. The doctor sent Pifer to James McCaugham, the same doctor who encouraged Johnson & Johnson to keep Photofrin alive.

Over the course of an 11-day hospital stay, McCaugham removed much of the tumor from her bronchial tubes using photodynamic therapy. Only once did she have any important side effects — an awful sunburn on the backs of her hands. Two years ago, at her last check-up, Betty was cancer free.

At 71, Pifer is active in a Bible group with her congregation in Lima, Ohio. Two or three times a week, she swims at a local pool.

She says, "The good Lord has given me six years of life. I thank him every day. I still could live 20 or 30 years more. To me, it's a miracle. I've seen a grandson born, and I've also seen a great-grandson born."

This complex process of drug development, ultimately, is about people like Betty Pifer. Thanks to Thomas Dougherty, James McCaugham and others, she might well be completing a lap at the "Y" as you read this.

My own personal stake in all this came as something of an afterthought. As I dove into the research, I remembered how my father, a pharmacist, died of a disease in 1975 for which a cure was found a few months earlier.

To this day, the smells of manufactured sterility that permeate drugstores always remind me of him, and I frequently smile when I smell them. From him, I inherited a love of Yellowstone and a disposition that tends to hold things in rather than express them loudly. While such quiet was endearing, it also led to stomach ulcers. My father's ulcers came from the pressures of a young family and the challenges of starting a small business. Ultimately, the ulcers bled and, in 1969, doctors cut out three-fourths of Dad's stomach to save his life.

The pictures I see of him today show a gaunt man in pain. I don't remember that. I remember my father knew duty. He rarely complained and went to work the day after Christmas 1975. I sat in his yellow chair when he came home early that night. He changed from his white pharmacist's jacket into green pajamas and headed to bed. I went to my room also, but couldn't sleep. My mother soon called the paramedics. I sneaked to the end of the hall past 25 pictures of me and my siblings to glimpse the efforts to save him. The efforts didn't look hurried. It seemed forbidden for a child to watch, though no one said anything or, in fact, even saw me. Still, I went back to my room after no more than a dozen seconds. I watched the paramedics rushing his gurney down the hallway.

My father was already low on blood when the paramedics arrived. As they struggled to give him a transfusion, his veins collapsed one-by-one under the strain of previous needle infusions. The bleeding ulcers won. My father died before he could reach the hospital.

At the same time, an amazing race to save my father and thousands of others like him was underway. Doctors in England with Smith, Kline & French believed that ulcers might be battled with a new kind of antihista-

mine. The theory seemed sound, but results were slim for nearly a decade. Then, in 1972, metamide was developed and entered clinical trials. Later, cimetidine came along.

In 1974, doctors made a decisive decision. A patient with bleeding ulcers was dying in the metamide test. Metamide had helped, but, as it often did, caused his white blood cell count to drop dangerously. Doctors decided to try cimetidine in the desperate hope it would save the patient's life.

It was a bold move. The research had survived one corporate restructuring and this was no time for another failure. Cimetidine worked and the patient was living a healthy life 17 years later, a medical journal says. By 1978, cimetidine was approved in the United States for ulcers under the brand name Tagamet. For their efforts, the drug's developer won the Nobel Prize.

Somewhere along the line, I got the mistaken notion that the FDA had delayed this research, and, therefore, had a hand in my father's death. The FDA slowed the study because of the real concern the effects on the immune system, but it did not stop the study. Instead, fate killed my father. Scientists looked at a precursor to metamide early on in the research, but noticed no effect. If they had noticed the effect, which was there, they might have saved a couple years. Those years might have made a difference.

In the end, there were no easy answers. The FDA sometimes stands in the way of good research and that costs lives. Still, the FDA rides a fickle pendulum trying to find the right balance. Like Hutt, I believe NOP ideas would be a good step, but I'm not sure if anyone really knows the best way to completely solve our clinical trial conundrum. I'm not sure how much risk the society is willing to take, nor do I know exactly what balance might have saved my father.

What I do know is this: I really miss him.