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THE NEW FDA

BRIAN WALSKI / Los Angeles Times

Tina and Jeffrey A. Englebrick of Shawnee, Kan., mourn their 3-month-old son, Scott, who died in 1997 after taking the heartburn drug Propulsid. The FDA "took my kid as a guinea pig to see if it would work," Jeffrey Englebrick says.

How a New Policy Led to Seven Deadly Drugs

■ **Medicine:** Once a wary watchdog, the Food and Drug Administration set out to become a 'partner' of the pharmaceutical industry. Today the public has more remedies, but some are proving lethal.

By DAVID WILLMAN
TIMES STAFF WRITER

WASHINGTON—For most of its history, the United States Food and Drug Administration approved new prescription medicines at a grudging pace, paying daily homage to the physician's creed, "First, do no harm."

Then in the early 1990s, the demand for AIDS drugs changed the political climate. Congress told the FDA to work closely with pharmaceutical firms in getting new medicines to market more swiftly. President Clinton urged FDA leaders to trust industry as "partners, not adversaries."

The FDA achieved its new goals, but now the human cost is becoming clear.

Seven drugs approved since 1993 have been withdrawn after reports of deaths and severe side effects. A two-year Los Angeles Times investigation has found that the FDA approved each of those drugs while disregarding danger signs or blunt warnings from its own specialists. Then, after receiving reports of significant harm to patients, the agency was slow to seek withdrawals.

According to "adverse-event" reports filed with the FDA, the seven drugs were cited as suspects in 1,002 deaths. Because the deaths are reported by doctors, hospitals and others on a voluntary basis, the true number of fatalities could be far higher, according to epidemiologists.

An adverse-event report does not prove that a drug caused a death; other factors, such as preexisting disease, could play a role. But the reports are regarded by public health officials as the most reliable early warnings of danger.

The FDA's performance was tracked through an examination of thousands of pages of government documents, other data obtained under the Freedom of Information Act and interviews with more than 60 present and former agency officials.

The seven drugs were not needed to save lives. One was for heartburn. Another was a diet pill. A third was a painkiller. All told, six of the medicines were never proven to offer lifesaving benefits, and the seventh, an antibiotic, was ultimately judged unnecessary because other, safer antibiotics were available.

The seven are among hundreds of new drugs approved since 1993, a period during which the FDA has become known more for its speed than its caution. In 1988, only 4% of new drugs introduced into the world market were approved first by the FDA. In 1998, the FDA's first-in-the-world approvals spiked to 66%.

The drug companies' batting average in getting new drugs approved also climbed. By the end of the 1990s, the FDA was approving more than 80% of the industry's applications for new products, compared with about 60% at the beginning of the decade.

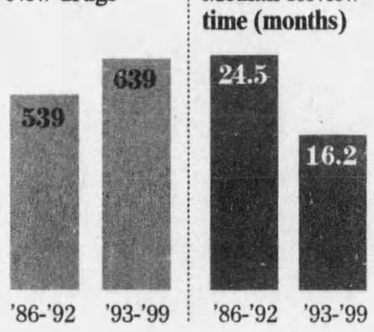
And the companies have prospered: The seven unsuccessful drugs alone generated U.S. sales exceeding $5 billion before they were withdrawn.

Once the world's unrivaled safety

Please see FDA, A6

The Effect

New drug approvals are rising as review time drops:



Source: FDA; Researched by JANET LUNDBLAD / Los Angeles TImes

Los Angeles Times

MORE INSIDE

Deadly Drugs: A catalog of dangerous prescription medications and how each was approved by the Food and Drug Administration, **A8**

Once Unthinkable: After decades, thalidomide has been approved for use in the United States, and now some fear that it could be misused, **A11**

Brace for Higher Electricity Bills, Governor Warns

■ **California:** Utilities also will have to bear some of the burden of spiraling costs for power, Davis says. Southern California Edison says it faces bankruptcy.

By DAN MORAIN, MITCHELL LANDSBERG and NANCY VOGEL
TIMES STAFF WRITERS

More than 20 million California consumers can soon expect to be hit with bigger electricity bills, Gov. Gray Davis acknowledged Tuesday, as the big utilities increased pressure on state and federal officials to rescue them from the ravages of a runaway energy market.

On a day in which the state's energy resources were once again strained to near their breaking point, Davis said in Sacramento that consumers would have to "bear some of the burden" of saving the utilities but that he hoped to cushion the blow.

It was a message that ratepayers had been assured they would not be hearing this soon after California deregulated its electricity market in 1996.

The utilities, stunned by rocketing wholesale energy prices, have painted a grim picture of the alternative and have called for a rate increase of more than 10%.

In the strongest warning it has issued yet, Southern California Edison claimed Tuesday that it is teetering on the brink of bankruptcy and will fail financially as early as next month if it is not granted relief by the state Public Utilities Commission, which is meeting in San Francisco on Thursday.

State officials said the PUC is unlikely to grant relief immediately to Edison and Pacific Gas & Electric, the state's two biggest utilities, but might do so next month when Davis is expected to appoint a new member to the commission, giving the governor a three-member majority.

Still, with consumer advocates fiercely opposed to an increase, and the legislature preparing to get involved, the scene appears set for an explosive political battle before the utilities are granted what one consumer lawyer called "a ratepayer bailout."

The rate hike would not affect customers of the Los Angeles Department of Water and Power nor other municipally owned utilities that are effectively exempt from

Please see POWER, A14

As Rate Hikes Loom, PR War Is Heating Up

By MIGUEL BUSTILLO and DAN MORAIN
TIMES STAFF WRITERS

SACRAMENTO—As electricity rate hikes loom for millions of California consumers, Gov. Gray Davis and the state's three major utility companies are waging an intense war to win over public opinion.

Casting themselves as victims in a deregulation experiment gone sour, utility officials are working feverishly to persuade the public, politicians and government regulators that re-regulation and rate increases are needed to cover their ballooning debt.

At the same time, Davis is engaged in damage control as he works to manage the biggest crisis of his administration, and ponders the unhappy prospect of presiding over rate hikes for customers and bankruptcy of some of the state's largest employers.

At each opportunity, Davis points out that he inherited the situation, and that he has no control over the key players—companies that own the bulk of the power plants that supply California, and have been charging dramatically high wholesale prices to Southern California Edison, PG&E and San Diego Gas & Electric Co.

Nor does he control the once

Please see ANALYSIS, A14

Federal Reserve Now Fears 'Weakness' Over Inflation

By PETER G. GOSSELIN
TIMES STAFF WRITER

WASHINGTON—The Federal Reserve demonstrated Tuesday how far the nation's once-booming economy has slipped by officially replacing its worry about growth-spurred inflation with fear of "economic weakness."

Although the central bank's policymaking Federal Open Market Committee stopped short of cutting interest rates to buoy growth, it signaled that it is ready to do so, perhaps even before its next meeting Jan. 30-31.

The panel's decision to leave the federal funds rate—which banks charge each other for overnight loans—at 6.5% disappointed embattled investors and sent the stock market tumbling.

But analysts said the Fed statement accompanying the rate decision represented a lightning-fast reversal for a central bank that has consistently worried about too much growth, not too little, over the last two years.

"Eroding consumer confidence, reports of substantial shortfalls in sales and earnings and stress in some segments of the financial markets suggest that economic growth may be slowing further," the statement said.

"That's a 180-degree turnabout from where the Fed was at its last meeting," said Robert V. DiClemente, chief U.S. economist with Salomon Smith Barney in New York. At that Nov. 15 session,

Please see PANEL, A5

Airbus Super-Jumbo Jet OKd in Challenge to Boeing

■ **Aerospace:** The news quickly ripples across the Atlantic and threatens to lead to a trade war.

By PETER PAE
TIMES STAFF WRITER

Shareholders of Airbus Industrie on Tuesday approved production of the world's largest airliner, taking dead aim at Boeing Co.'s decades-long monopoly of the market for large commercial aircraft and threatening to touch off a major trade dispute with the United States.

In a bold strategy to control one of the most lucrative exports in the world, the European-based consortium is risking $11 billion to develop the super-jumbo plane. When it enters service in early 2006, the jetliner that can seat up to 800 passengers will dwarf the largest aircraft available today, the venerable 420-seat Boeing 747.

By virtue of its sheer size, the super-jumbo jet—dubbed the A380—also promises to usher in a new era of air travel, much the way the 747 did when it was introduced more than 30 years ago. The double-decker A380 will have communal space for a casino, a children's playroom and a gymnasium.

"Airbus has a new flagship," said Manfred Bischoff, chairman of the world's second-largest airplane maker, based in Toulouse, France. "We are convinced that this aircraft will have a bright and extremely successful future."

But the much anticipated decision was overshadowed somewhat by an international spat that

Please see AIRBUS, A5

INSIDE TODAY'S TIMES

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Clinton to Issue Sweeping Patients' Privacy Rules

■ **Health care:** Measure would prohibit sharing of all medical records except for treatment and payment.

By ALISSA J. RUBIN
TIMES STAFF WRITER

WASHINGTON—After years of fruitless congressional efforts, the Clinton administration today will issue the first comprehensive regulations protecting the privacy of patients' medical records.

The rules prohibit doctors, hospitals, HMOs and other health providers from sharing patients' medical records—except for treatment and payment.

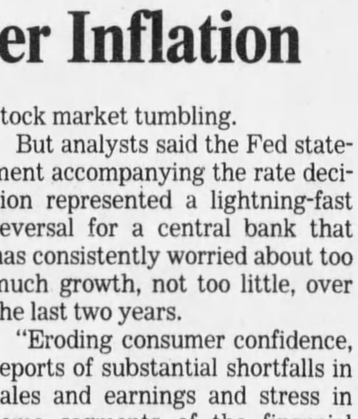
The new measure—considerably broader than earlier versions—covers all records, not just those stored electronically. It also strengthens the provisions that limit employer access to medical data.

"The new rules will apply to all health insurers and virtually every health care provider . . . and it will give patients' more control over and access to their medical records," said Chris Jennings, chief health care advisor to President Clinton.

The president, however, will emphasize when he unveils the regulations that more needs to be done to guarantee the privacy of patients' records. He will argue for additional legislation requiring that life insurers and worker compensation programs also safeguard patients' records—and that consumers should have a right to sue providers who violate the medical confidentiality rules.

The privacy regulations were

Please see PATIENTS, A5



Associated Press

Bush Pays Visits to Clinton, Gore

President-elect George W. Bush returned to his father's houses to call on outgoing President Clinton and his campaign opponent, Vice President Al Gore. **A4**

THE NEW FDA

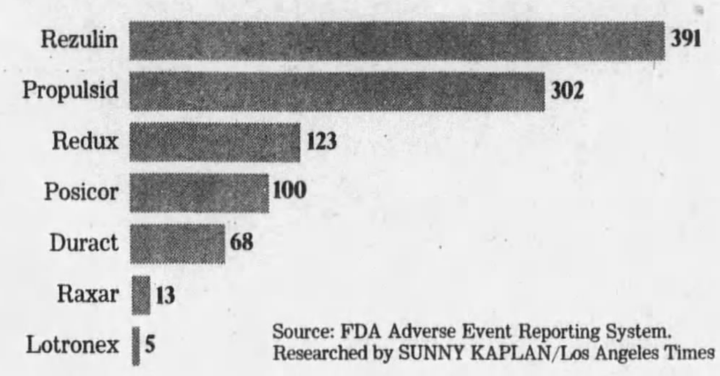
CASE STUDIES

Drug After Drug, Warnings Ignored

Danger signs were present as each of the prescription medicines on the following pages were considered for the FDA's approval. Even so, top administrators moved ahead, often leaving doctors to assume the risks listed in fine-print labels. Seven were eventually withdrawn, but only after reports of deaths.

Reported Deaths

Total fatalities in which these prescription drugs were cited as suspects.



Source: FDA Adverse Event Reporting System.
Researched by SUNNY KAPLAN/Los Angeles Times

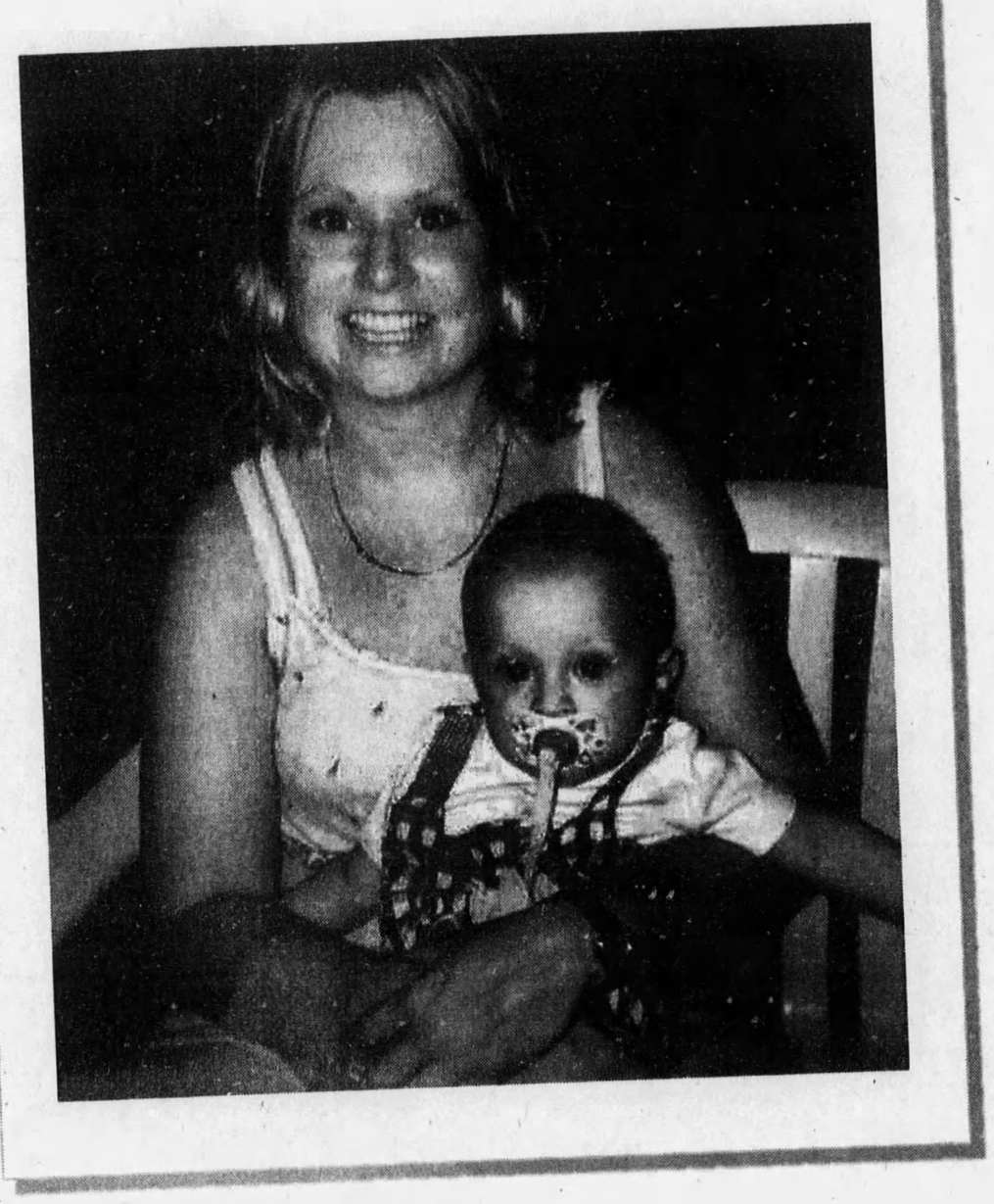
PROPULSID

A Heartburn Drug, Now Linked to Children's Deaths

Once evidence of harm emerged, FDA took years to withdraw approval

"Those of us here at the FDA who are aware of your loss wish to again extend our deepest sympathy and sincere condolences to you and your family."

—FDA Administrator Florence Houn, writing July 27, 2000, to the mother of 9-month-old Gage E. Stevens, who died on Thanksgiving 1999.



Gretchen Stewart holds her son, Gage Stevens, who was 9 months old when he died after being given Propulsid as part of a pediatric study. The county coroner concluded that Propulsid was a factor in his death.

In mid-1993, FDA officials prepared to approve Propulsid, a drug that eased nighttime heartburn. But a sign of danger loomed.

FDA medical officer Andre Dubois noted that 48 of 1,993, or 2.4%, of the patients who took Propulsid in U.S. studies experienced "heart rate and rhythm disorders." In addition, eight children age 6 or younger who were given Propulsid had died.

Dubois found that the drug's chemical makeup could disturb cardiac function. But he agreed with drug maker Janssen Pharmaceutica, a Johnson & Johnson Co. subsidiary, that the deaths in the studies were attributable to other causes.

He recommended approval along with disclosure in the label of potential cardiac effects. "The risk seems very low," he said.

Dubois, however, worked in a division that focuses on drugs for the gastrointestinal tract.

No one at the FDA consulted with the agency's division of cardiac specialists before approving Propulsid on July 29, 1993, according to physicians familiar with the matter. By not tapping their expertise, FDA officials failed to notice what should have been another warning flag: Electrocardiograms showed that Propulsid prolonged patients' "QT interval," the time during which the heart's main pumping chambers contract and then relax.

If the QT interval—typically about 4/10 of a second—is extended even slightly, it can trigger a disruption or cessation of the heartbeat. Called an arrhythmia, it can result in sudden death.

FDA officials outside the gastrointestinal division had already warned publicly—on June 11, 1990—that two allergy drugs, Seldane and Hismanal, prolonged the QT interval and therefore posed lethal risk. Both drugs were later withdrawn.

Indeed, the danger had been stressed for several years by Dr. Raymond J. Lipicky, director of the agency's cardiology division. Lipicky, writing in the August 1993 issue of the American Journal of Cardiology, said if a drug that prolonged the QT interval had a benefit that was "less than lifesaving ... any risk of death would likely be considered unacceptable."

In approving Propulsid, the FDA agreed to labeling that advised doctors of "rare cases" of increased heartbeats. The labeling said Propulsid's role in the events "was not clear."

In response to written questions, Dr. Janet Woodcock, director of the FDA's drug review center, said the danger associated with non-cardiac drugs that prolonged the QT interval "was not well appreciated" at the time Propulsid was approved. Consequently, she said, this "was not identified as a concern" by the gastrointestinal division.

By early 1995, Propulsid's danger to the heart was certainly identified as a concern within the gastrointestinal division, agency records show.

On Jan. 25, 1995, a senior FDA medical officer, Dr. Stephen B. Fredd, told Janssen executives that recent adverse-reaction reports showed their drug was prolonging the QT interval, perhaps resulting in deaths.

According to the meeting summary, "It was the firm's position that the cases cited by Dr. Fredd were not 'clean' cases, thus making it difficult to attribute the effect to [Propulsid]." Fredd responded that "unequivocal evidence" of Propulsid's culpability was unlikely to be captured outside of a controlled clinical study.

But within a month, the FDA and the company agreed to the first of five safety-labeling changes that would help keep the drug on the market over the next five years.

Meanwhile, a significant market for Propulsid emerged in the treatment of children.

Propulsid was never proved effective or safe for infants, yet it became the drug of choice for many pediatricians in treating gastric reflux, a common disorder that is usually outgrown by age 1. Reflux can impede infants' digestion and, due to their crying, disrupt their parents' sleep. As with almost all drugs, doctors could lawfully prescribe Propulsid for any use, or "indication," they chose.

On Aug. 15, 1996, the FDA informed the Johnson & Johnson subsidiary that Propulsid was "not approvable" for children, interviews and documents obtained by The Times show. The rejection, in keeping with FDA practice, was not made public.

In private correspondence a year later, on Aug. 19, 1997, Dr. Lilia Talarico, FDA's gastrointestinal drugs division director, cited "at least" three recently reported deaths among child patients. She told a company official the agency was considering altering the label of Propulsid to "contraindicate," or to warn against its use in infants.

Asked why the FDA did not immediately inform doctors and patients of the deaths, Woodcock told The Times: "Labeling changes [advising of infant deaths] were requested by FDA in August of 1997 but were not agreed to by the company until June of 1998."

That revised label did acknowledge "several pediatric deaths" but left physicians guessing whether Propulsid was the culprit, saying, "Causality has not been established."

Parents of children who died after taking Propulsid said in interviews that they had no inkling of danger.

"If I had known that this drug caused cardiac arrhythmias, I would never have given it to him," said Tina Englebrick, the mother of 3-month-old Scott, who died in October 1997. The Kansas health department identified Scott's cause of death as sudden infant death syndrome.

Had the parents of Gage Stevens, the deceased 9-month-old, "been informed of a risk of sudden death, they would not have administered the medication to their son," according to a lawsuit they filed in a Pennsylvania court on Sept. 10 against the manufacturer and the doctor and hospital who treated him. Gage, who had reflux, was given Propulsid within a pediatric study that was approved by the FDA and performed by researchers at the University of Pittsburgh.

> **'This isn't as if it's some *mystery*. ... They evaluated this and came to their own conclusions about the risks.'**

He died at 6:30 a.m. on Thanksgiving 1999. The county coroner concluded that the death was "directly related" to Propulsid and one other drug administered to the child. The coroner said Gage "most probably" had died after suffering a cardiac arrhythmia.

Said Dr. Robert R. Fenichel, who retired this year as deputy director of the FDA's cardiac drugs division: "It was scandalous that all of these kids were being treated with [Propulsid]," in the absence of proven safety and effectiveness.

On March 23, 2000, the FDA announced that Propulsid would be taken off the market as of July as a normally prescribed drug because of scores of confirmed heart-rhythm deaths. Overall, Propulsid has been cited as a suspect in 302 deaths.

FDA administrators now concede that the agency failed to contain Propulsid's fatal risk.

"We've had a seven-year history with this drug where it's a very rich opportunity for us to learn," the FDA's Dr. Florence Houn told drug industry officials in a Webcast on June 22. "One of the things we have learned is the approved indication for a drug really needs to [justify] the serious and life-threatening" side effects.

In comments the same month to an FDA advisory committee, Houn added, "The labeling probably was not effective."

Why did the agency wait so long to seek the withdrawal of this drug for nighttime heartburn in adults?

"We simply tried a variety of measures," Woodcock said in an interview. "We have to sort of walk that line: Where do we inform and where do we intervene by removing a drug from the market? That is a very draconian step.... And so, we do try to avoid that."

Six specialists involved with the FDA's decisions concerning Propulsid said the volume of prescriptions for reflux in infants helped keep the drug on the market.

One specialist who sought earlier withdrawal of Propulsid said, "If it were just the nocturnal heartburn indication we were considering ... it's a pretty easy decision" to pull it off the market. Many alternative therapies existed, including over- the-counter products like Tums, Maalox and Zantac.

Woodcock, who was appointed to her position 10 months after Propulsid was approved, said the FDA did not formally weigh the off-label use while deciding to keep the drug on the market. She acknowledged that it was prescribed widely for children but said she relied on pediatricians to make prudent decisions.

"They're aware of the QT-prolongation issue," Woodcock said. "This isn't as if it's some *mystery*. ... They evaluated this and came to their own conclusions about the risks."

A spokesman for the Johnson & Johnson subsidiary, Greg Panico, said the company did not promote Propulsid for use by children. However, he acknowledged that it did make two "educational grants" to the North American Society for Pediatric Gastroenterology and Nutrition. The society's literature advised doctors that Propulsid could be used safely and effectively in children.

Panico declined to say how much money the company provided; according to the society's Web site, the group has been "generously supported" by the Johnson & Johnson subsidiary. The society held a symposium on the use of Propulsid at an October 1998 conference in Orlando, Fla. A spokeswoman for the pediatric society said the company's grants came with "no strings attached."

The removal that Woodcock and her aides negotiated this year allows the continued sale of Propulsid under a "limited access plan." This authorizes doctors to administer the drug to patients of all ages who have not benefited from other treatments and who would be closely monitored.

In September, the British Medicines Control Agency rejected continued sales of Propulsid there under such conditions, saying, "Restricted-access schemes ... are not adequate to protect public health." The British have warned since 1998 against any use of Propulsid in infants and cautioned against prescribing it to children up to age 12.

For her part, Woodcock said she remains "concerned" about the drug's use among children. A recent agency review found that, while "no clear evidence" implicated Propulsid as the primary cause of eight children's deaths before the July 1993 approval, neither was there enough data to exclude a "role" for the drug in several of those cases.

As for adult patients who died, Woodcock said, "It's a terrible thing to happen to somebody who is just taking the drug for heartburn."

Panico said there remains a place for Propulsid.

"When we made the decision to limit access to the drug, we had pleas from families of children who are taking this drug to make sure that these kids can have continued access to it," he said. "So, it's a balancing act."

Regarding one of those patients, a 68-year-old man who died a week after completing the clinical trial, Meyerhoff wrote: "This patient may have been at higher risk for [fatal] arrhythmia due to QT interval prolongation from grepafloxacin," the chemical name of Raxar. The second patient died five days after withdrawing from the clinical trial.

She added in her review, dated November 1997: "Again it is not clear that this event is unrelated to [Raxar]. Sudden death in a patient with no prior cardiac history is suggestive of an arrhythmia.... The label will need to have an adequate warning regarding the possibility of QT prolongation." Overall, she found a "significantly higher" rate of adverse events among patients who had taken 600 milligrams compared with lower doses.

With Meyerhoff's assent, the FDA approved Raxar for treating bronchitis, pneumonia, urinary tract infections and gonorrhea. The drug's label stated that "prolongation of the QT interval has been observed in healthy volunteers receiving Raxar."

But the label did not disclose the fatalities described in Meyerhoff's review. It said that "there were no deaths or permanent disabilities" among those who took Raxar in 400-milligram doses. The statement was true, if incomplete: All four of the study patients who died took Raxar in 600-milligram doses. And Glaxo marketed the drug at doses of 200 milligrams, 400 milligrams and 600 milligrams. A total of 925 patients took the 600-milligram dose in the clinical studies.

On Oct. 27, 1999, Glaxo pulled Raxar off the market.

In a subsequent letter to doctors, Glaxo said that because of Raxar's effect on "QT interval prolongation" the drug was unacceptably risky. In a separate statement, the company said it "is no longer convinced that the benefits of Raxar outweigh the potential risk to patients, given the availability of alternative antibiotics."

Records filed with the FDA show that Raxar was cited as a suspect in the voluntarily reported deaths of 13 patients. They ranged in age from 42 to 86; most of them were under 70.

"[Raxar] goes on the market, kills people and has to come off," said Dr. Raymond L. Woosley, the pharmacology department chairman at Georgetown University who served on an FDA advisory committee in the 1980s. "It had been proven, over and over, that this QT prolongation predicts terrible events."

By the time of the withdrawal, Raxar had generated $23.5 million in U.S. sales. Securities analysts had predicted it could be a $1-billion drug.

With so many other antibiotics on the market, why did the FDA expose patients to the risk of Raxar?

In a written response to questions, Woodcock indicated that the FDA sought to address the drug's cardiac risk through precautionary language in its labeling.

Asked why that labeling did not acknowledge the deaths of patients who took doses of 600 milligrams, Woodcock wrote that none of the fatalities "was shown to be attributable to Raxar."

In an interview over the summer, Woodcock said the FDA's patience was gone for new drugs that prolong the QT interval. "We're encouraging people, if there's QT prolongation, don't develop it," she said.

This would mark a turnabout.

Just last December—less than two months after the withdrawal of Raxar—the FDA approved a new antibiotic, called Avelox, despite the drug's well-documented propensity in clinical studies to prolong the QT interval.

Please see DRUGS, A9

RAXAR

Warning on Label Omits Deaths

Heart problems were mentioned in fine print, but not key dosage data.

When the antibiotic Raxar was approved on Nov. 6, 1997, FDA officials knew that it too might cause irregular rhythm and stop a patient's heart.

An agency medical officer, Dr. Andrea N. Meyerhoff, suspected that two of four patients who died after taking Raxar in clinical trials possibly suffered heart-rhythm disturbances caused by the drug.

Meyerhoff noted in her review that the drug manufacturer, Glaxo Wellcome Inc., said Raxar played no role in the deaths. But Meyerhoff wrote that the two cases posed an open question. Each patient who died had taken 600-milligram doses.

THE NEW FDA

CASE STUDIES

DRUGS: Continued From A8

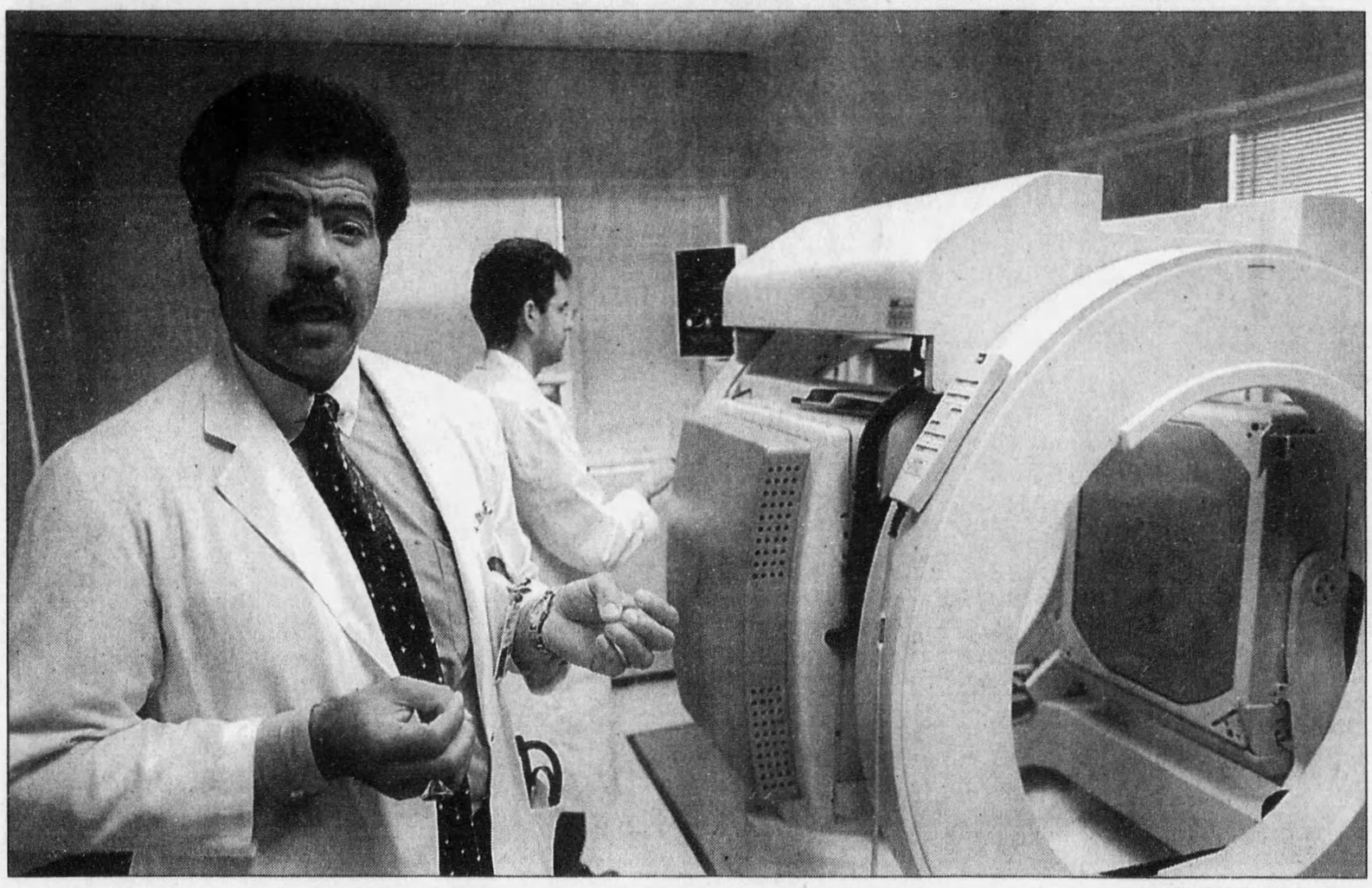
Avelox was approved for treating sinus infections, bronchitis and pneumonia.

On the 267th line of the Avelox label, doctors are warned in bold type that it "has been shown to prolong the QT interval."

So far, Avelox, made by Bayer Corp., has been prescribed for more than 300,000 patients in the U.S. The drug has been cited as a suspect in 18 deaths here and abroad. A Bayer spokesman, Robert Kloppenburg, said that the company does not believe any of the fatalities were "attributable" to Avelox and that most of the patients had serious preexisting conditions.

Avelox, he said, holds an advantage over many antibiotics because it need only be taken once daily for five days to be effective against bronchial infections. Securities analysts predicted in February that Avelox would generate sales topping $1 billion within three years.

Woodcock said the FDA approved Avelox because "the extent of QT prolongation ... was too small to pose a significant risk in the face of the benefits." She noted that an agency advisory committee recommended approval and said that "a conservative approach was taken in the label."



PATTY WOOD/For The Times

University of Texas physician Lemuel A. Moye, who served in the late 1990s on an FDA advisory committee, says of the agency: "They've lost their compass and they forget who it is that they are ultimately serving. Unfortunately the public pays for this."

REDUX

Unheeded Warnings on Lethal Diet Pill

Heart damage causes billions of dollars in potential legal liability.

Before coming to the FDA as a medical officer in 1989, Dr. Leo Lutwak had specialized in the fields of obesity and osteoporosis as a Cornell University professor, as a drug company consultant and as a practicing physician. He said he hired on at the FDA because he relished the scientific challenge of new drugs and the call of public service.

In 1995, Lutwak was the lead FDA medical officer reviewing the diet drug Redux, which in one pill approximated half of the now-infamous slimming cocktail known as fen-phen.

Both Lutwak and his boss, Dr. Solomon Sobel, told The Times that they resisted the approval of Redux.

"I, as the primary reviewer, felt that the drug had low effectiveness and very high risk for neurotoxicity and pulmonary hypertension," a disorder that damages the respiratory system, Lutwak said.

"I was insisting on a black box," he added, referring to the bold border at the top of a prescription label that alerts doctors and patients to severe life-threatening risk. "But the management accepted the company's arguments against the black box. And I don't know why."

Sobel, director of the FDA's endocrine and metabolic drugs division throughout the 1990s and who remains at the agency, was concerned that Redux did not work. He said he refused to sign the agency's formal letter of approval.

"Well let me tell you," Sobel said. "I was supposed to sign off on that letter.... I told [an FDA administrator, Dr. James] Bilstad that I would not sign on it. If he wanted to approve it, he should sign on it. And the record shows, he's the one who signed on it."

How Redux came to be approved in April 1996 remains a curiosity.

After an FDA advisory committee voted, 5 to 3, that evidence of Redux's safety was "not sufficient to warrant approval," Bilstad took the unusual step of scheduling a second meeting, just two months later. At that meeting, in November 1995, the committee voted, 6 to 5, to recommend approval.

Lutwak said he was "shocked" by the scheduling of the second meeting.

Much was riding on Redux. Analysts at one securities firm, Rodman & Renshaw, estimated the drug would gross $1.8 billion within four years.

But Redux was withdrawn on Sept. 15, 1997, after heart valve damage was detected in patients put on the drug. Civil lawsuits that are now pending also allege that Redux caused the potentially fatal respiratory disorder that had worried Lutwak.

American Home Products Corp., which marketed Redux and Pondimin, a diet pill that was used widely in formulations of fen-phen, agreed last fall to pay or set aside $4.75 billion to settle lawsuits related to the drugs' potential to cause heart valve damage. The company more recently has set aside up to an additional $4.75 billion to pay other patients who have suffered from the respiratory condition or heart valve damage.

"We are aggressively settling as many cases as we can," said Douglas Petkus, a spokesman for Wyeth-Ayerst Laboratories Inc., a subsidiary of American Home.

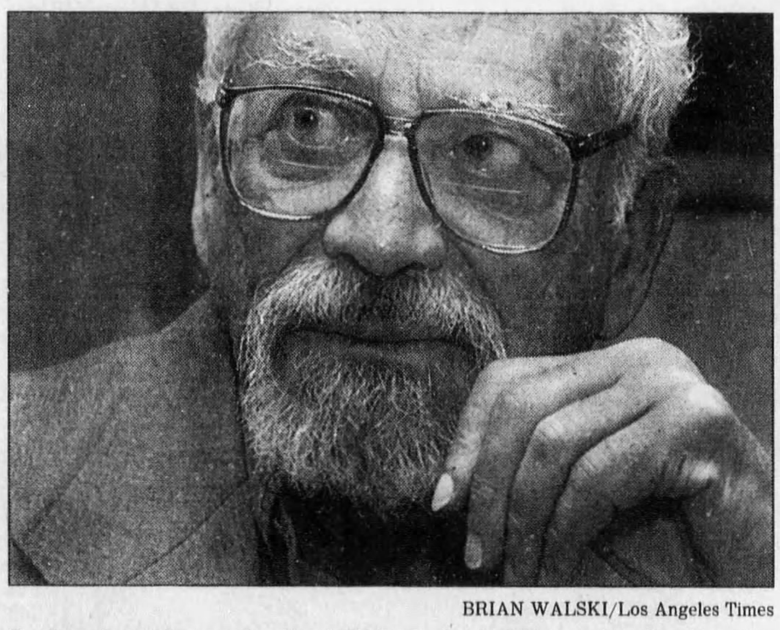
In its one year on the market, Redux generated sales of $255.3 million. The FDA received reports before and after the withdrawal that cited Redux as a suspect in 123 deaths.

Bilstad, who left the FDA in January, declined to be interviewed this fall when reached at his home.

In a written statement, Woodcock acknowledged that "the possibility of including a black box warning" on Redux's label was discussed with Wyeth-Ayerst. But, she said, FDA officials decided "it was not warranted." She said that the drug's potential respiratory risk was noted within the labeling in bold type. Before Redux went on the market, Woodcock said, "there was no hint" that it would cause heart valve damage.

Lutwak, now 72, said he regrets the approval of Redux—and the agency's failure to insist on a black box warning.

"It might have saved lives," he said.



BRIAN WALSKI/Los Angeles Times

Dr. Leo Lutwak was the lead FDA medical officer reviewing the diet drug Redux, which in one pill approximated half of the slimming cocktail known as fen-phen. He said he resisted its approval.

DURACT

After Just 10 Days, Painkiller Posed Risk

Drugmaker's lobbying won fine print instead of prominent warning.

The FDA medical officers who reviewed a proposed painkiller called Duract saw the problem from the outset: Too many patients who took the pill in clinical trials suffered liver injury.

"It seems imprudent to open the doors to extensive use when there have been early warning signs," an FDA medical officer, Dr. John E. Hyde, wrote on July 31, 1996. He said the specialists reviewing Duract "were concerned about the frequency and severity" of the injuries reflected in patients' blood tests.

Hyde and a colleague, Dr. Rudolph M. Widmark, concluded in another report: "The [liver] toxicity is a significant concern with this drug."

Believing that the risk increased the longer a patient remained on Duract, they sought to rid the label of any reference to long-term use. They also proposed a prominent black box warning regarding Duract's liver toxicity.

This was not what the manufacturer, Wyeth-Ayerst Laboratories had in mind.

"They were unhappy with my review," Widmark said in an interview.

In a market already stocked with more than 20 prescription and over-the-counter painkillers, a black box warning could turn off doctors and cripple sales.

Wyeth-Ayerst took its case to Widmark's superiors. Widmark responded, in a memo dated Nov. 14, 1996, to the FDA drug center's No. 2 administrator, Dr. Murray M. "Mac" Lumpkin:

"The company would like a label that actually puts the onus on the prescribing physician because if severe and maybe fatal liver toxicity [occurs], the physician will be sued and will be found liable if he/she did not 'monitor' for liver damage. Wyeth-Ayerst will be in the clear, because 'it is in the label.'"

Widmark added, "I hope that this short memo will help you to make the right decision in this dispute."

When the company rolled out Duract following the FDA's approval on July 15, 1997, there was no black box on the label. Securities analysts predicted that in four years Duract could yield annual sales topping $500 million.

Beginning on the 135th line, the label's fine print informed doctors that Duract was recommended for "generally less than 10 days." The label also advised that, "if a physician chooses to administer Duract for a longer duration," patients' liver functions should be checked after a month.

Seven months after Duract's market launch, the FDA and Wyeth-Ayerst responded to reports of severe liver damage: A black box was added.

The revised labeling also flatly warned doctors for the first time "not " to prescribe the drug for longer than 10 days.

"Patients using Duract for more than 10 days have developed jaundice, fulminant hepatitis and liver failure requiring transplants," the FDA said, announcing the label change.

By the time Wyeth-Ayerst announced Duract's withdrawal on June 22, 1998, the FDA had received 13 voluntarily filed reports of liver failure. The agency said that "almost all" of the cases occurred among patients who took the drug longer than 10 days.

Widmark, an Austrian immigrant, said he believes that lives would have been saved if FDA administrators had stood behind his original recommendation for a black box warning.

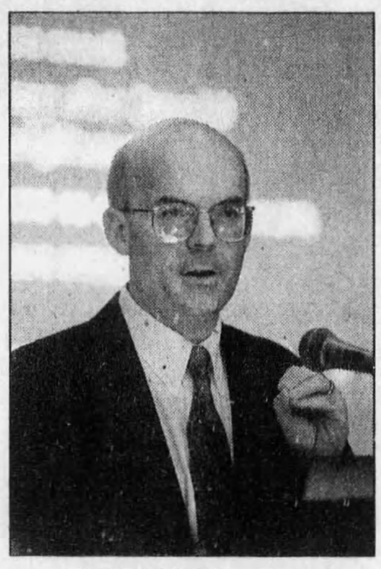
"I personally think yes," Widmark said. "They were more impressed with the company's consultants than they had confidence in their own reviewers....

"Something is wrong and something should be done to avoid this in the future."

Now 75, Widmark retired in December 1997 after spending 11 years with the FDA. He still works as a consultant to the pharmaceutical industry.

The spokesman for Wyeth-Ayerst, Petkus, said the company's consultants "made a case that there was no need for a black box," [COL.COUNT exceeded] End Page 1 of 2] believing the recommendation to use Duract generally less than 10 days was sufficient. The FDA's management, he said, agreed.

In their May 1999 medical journal article, Woodcock and Lumpkin said the problems that emerged with Duract were "unexpected," adding: "Given the availability of other analgesics with a wider margin of safety than [Duract], the FDA believed that the risk from this product outweighed its benefits."



JEFF MANKIE/Los Angeles Times

FDA senior administrator Dr. Murray M. "Mac" Lumpkin wrote about "unexpected" problems with the prescription medications Duract and Posicor.

In a written response to questions, Woodcock said, that if used short term, "it was felt that Duract would not cause liver damage more often than" certain other painkillers. She said the findings of potential danger, identified in advance by the agency's two medical officers, involved tests that "do not always signal clinically important [liver] toxicity."

By late 1998, the FDA had received voluntary reports citing Duract as a suspect in 68 deaths, including 17 that involved liver failure. During its one year on the market, Duract generated sales totaling $89.7 million for Wyeth-Ayerst.

POSICOR

143 Sudden Deaths Did Not Stop Approval

With study results kept secret at first, nation got ninth blood-pressure drug.

Senior FDA officials with the power to approve new drugs were warned in advance about the dangers of Posicor, a pill for high blood pressure and symptomatic chest pain.

The clinical studies of Posicor "cast a shadow of potential risk for serious arrhythmias," FDA medical team leader Dr. Shaw T. Chen wrote on Dec. 18, 1996. The data in hand also showed Posicor would interact with certain other drugs, posing potentially severe risk.

A 70-year-old man suffered "sudden death" in one study of Posicor's effect on chest pain. The senior FDA officials also were told of sudden deaths in 142 other patients who took either Posicor or a placebo in an ongoing study focused on congestive heart failure. However, details from the 2,400-patient study remained sealed because the manufacturer opposed breaking the experiment's confidentiality until it was finished.

This left the FDA officials a choice: Wait a year or more, or approve Posicor without knowing the details.

"I sure don't feel good about what I've seen," said Dr. Lemuel A. Moye, a member of the FDA's Cardiovascular and Renal Drugs Advisory Committee that met on Feb. 28, 1997. Moye, a physician and biostatistician at the University of Texas, suggested it would be prudent to delay judgment until the study's results were unsealed. "I'm afraid that we are rushing into this.

According to a transcript of the meeting, Moye voiced concern about Posicor's effect on heart rhythm and its potential to interact with other compounds. "Patients will be taking this in fairly uncontrolled situations in combinations of drugs which have ramifications yet unknown," he said.

Another committee member, Dr. Robert Califf, professor of medicine at Duke University, said: "If this [drug] was really something that was dramatically different, better than anything else in the way of relieving symptoms, then I would look at it differently. But given the fact there are a lot of other effective therapies out there, why not be safe with the public?"

Indeed, scores of other drugs for treating high blood pressure were already on the market, and Posicor was not proved to offer lifesaving benefit.

The drug's manufacturer, New Jersey-based Hoffman-La Roche Inc., saw no need to delay.

"There is no signal that there is arrhythmic or potentially arrhythmic risk with the drug," said Roche's Dr. Isaac Kobrin, terming the sudden deaths of four patients in another study "a chance finding."

The committee voted, 5 to 3, to recommend approval of Posicor, with Califf and Moye in the minority.

After presiding over the five-hour discussion, the committee chairman, Dr. Barry M. Massie of San Francisco, abstained from voting amid a financial conflict: Massie was a co-investigator in Roche's ongoing study of Posicor. After that meeting, Roche hired him as a speaker for the drug, Massie acknowledges.

On June 20, 1997, the FDA approved Posicor.

Four days later, a Roche news release quoted Massie to buttress the company's claim that "the incidence of side effects was low" during clinical studies of Posicor.

Asked about this sequence of events, Massie said, "You do wonder how the world would perceive it. I'm glad I didn't vote, let's put it that way."

Doctors were cautioned in speck-sized type—beginning on the 278th line of the drug's label and again on the 365th about prescribing Posicor in combination with various medications, including allergy pills, tranquilizers, a sleeping pill and the heartburn drug Propulsid.

Authorities in Sweden in mid-1997 saw sufficient danger to keep Posicor off the market. But the U.S. approval spurred high hopes for Roche. Analysts at one brokerage firm, Salomon Smith Barney, projected sales of $2.9 billion within four years.

Six months after approving Posicor, the FDA advised doctors of the pill's "life-threatening" danger. The agency announced that it had "received reports of dangerously lowered heart rates in about 20 patients." Roche agreed to a label change—advising that Posicor should not be taken in combination with cholesterol-lowering drugs. This brought to 26 the number of drugs that doctors were warned not to prescribe with Posicor.

On June 8, 1998, Roche announced Posicor's withdrawal, citing "evolving information concerning the potential for drug interactions" and "preliminary results" from the ongoing heart failure study that had drawn the attention of the advisory committee.

The study, Roche said, showed that the patients gained "no overall" benefit from Posicor.

According to those familiar with the matter, the study also found that the patients given Posicor died at a rate about 10% greater than those who took a comparator. "It definitely did not look good," recalled Fenichel, who was then the cardiac drug division's deputy director.

Apart from the clinical research, records filed with the FDA show that doctors and others reported Posicor as a suspect in the deaths of 100 patients.

"Posicor should not have been approved," Moye said. "Therefore, any death that was attributable to Posicor was an unnecessary death."

The FDA's Woodcock and Lumpkin wrote in their May 1999 medical journal article that the problems that sunk Posicor also were "unexpected." Asked recently about this, Woodcock retreated slightly; she said that serious adverse reactions resulting from Posicor's interaction with one drug "perhaps could have been anticipated."

Overall, she said, the agency had hoped for better compliance with advice in the label to avoid the concomitant use of Posicor and the 26 other drugs it interacted with.

A spokesman for Roche, Martin Hirsch, declined to answer questions but said the company "demonstrated sound and responsible judgment in the way [it] developed, launched and marketed and withdrew Posicor. And we have cooperated with the FDA throughout."

LOTRONEX

Promised Drug Study Never Got Underway

'Irritable bowel' remedy pulled after reports of serious injuries.

Agency officials agreed in July 1999 to conduct a fast-track medical review of Lotronex, a pill from Glaxo Wellcome Inc. intended to treat irritable bowel syndrome in women. To justify such accelerated review, the FDA must find that the targeted disease is "serious."

Irritable bowel syndrome can result in abdominal pain and frequent trips to the bathroom. But it neither maims nor kills people.

An FDA medical officer, Dr. John R. Senior, discovered dur-

Please see DRUGS, A10

THE NEW FDA

CASE STUDIES

Warnings on Drugs Were Ignored

DRUGS: Continued From A9

ing the review that four Lotronex patients in clinical studies suffered a potentially life-threatening complication called ischemic colitis, which results from inadequate blood flow to the colon.

Senior, a former pharmaceutical industry executive and a gastrointestinal specialist, knew the rarity of ischemic colitis: Some physicians can practice for decades without treating a single case.

While some cases would be mild and reversible, Senior wrote, ischemic colitis "can be catastrophic."

Senior found other troubling results. He warned that 27% of the patients who took Lotronex in Glaxo's studies experienced constipation. He noted that not a single patient who took a placebo pill developed ischemic colitis and that only 5% of the placebo patients got constipated.

Glaxo representatives denied that Lotronex had caused the cases of ischemic colitis and said any risks could be adequately managed. But Senior warned of the potential for Lotronex patients to suffer debilitating bowel injuries or death.

If these were the risks, what were the potential benefits?

FDA reviewers found that Lotronex improved symptoms in only 10% to 20% of the patients. Still, an FDA advisory committee, whose participants included a paid consultant to Glaxo, unanimously recommended approval. (The yes vote voiced by the Glaxo consultant, Dr. Arnold Wald of Pittsburgh, was invalid, agency officials say, because of his status as a temporary appointee.)

The FDA had a choice: Withhold approval of Lotronex until Glaxo undertook a major safety study to assess the drug's link to ischemic colitis or approve the drug conditioned on a pledge by Glaxo to perform the study in the following year.

Top FDA officials chose not wait. They approved Lotronex on Feb. 9, 2000. The original labeling said that ischemic colitis had occurred "infrequently" in the clinical studies and that there was no way to predict which patient was at highest risk.

It was Lotronex's first approval worldwide. Securities analysts estimated it would generate sales of up to $2 billion within five years.

A spate of bowel injuries emerged quickly—consistent with Senior's fears.

In June, the FDA's Woodcock embraced the crafting of a "medication guide" aimed at advising patients of Lotronex's risks. But the leaflets were not delivered to pharmacies until late September. Meanwhile, Woodcock's staff proposed a black box warning for Lotronex's label but retreated when Glaxo publicly opposed the idea.

By October, 49 cases of ischemic colitis in Lotronex patients—including five deaths—had been reported to the FDA. Records show that no fewer than 91 patients were hospitalized, many with severe constipation. Several bowel surgeries, including the removal of a patient's colon, were performed.

FDA officials who had backed the approval of Lotronex maintained their support for the drug into November, but staff epidemiologists pointed to the surgeries and deaths and the likelihood that those voluntarily reported events were a small fraction of the true scope of harm.

They urged withdrawal.

Glaxo and the FDA announced on Nov. 28 that Lotronex would be pulled from the U.S. market. At that point, Glaxo's promised study of the drug's link to ischemic colitis still had not enrolled a single patient.

Asked why the FDA approved Lotronex, given the ischemic colitis risk, Woodcock indicated that her aides had believed Glaxo's view of the risk more than Senior's.

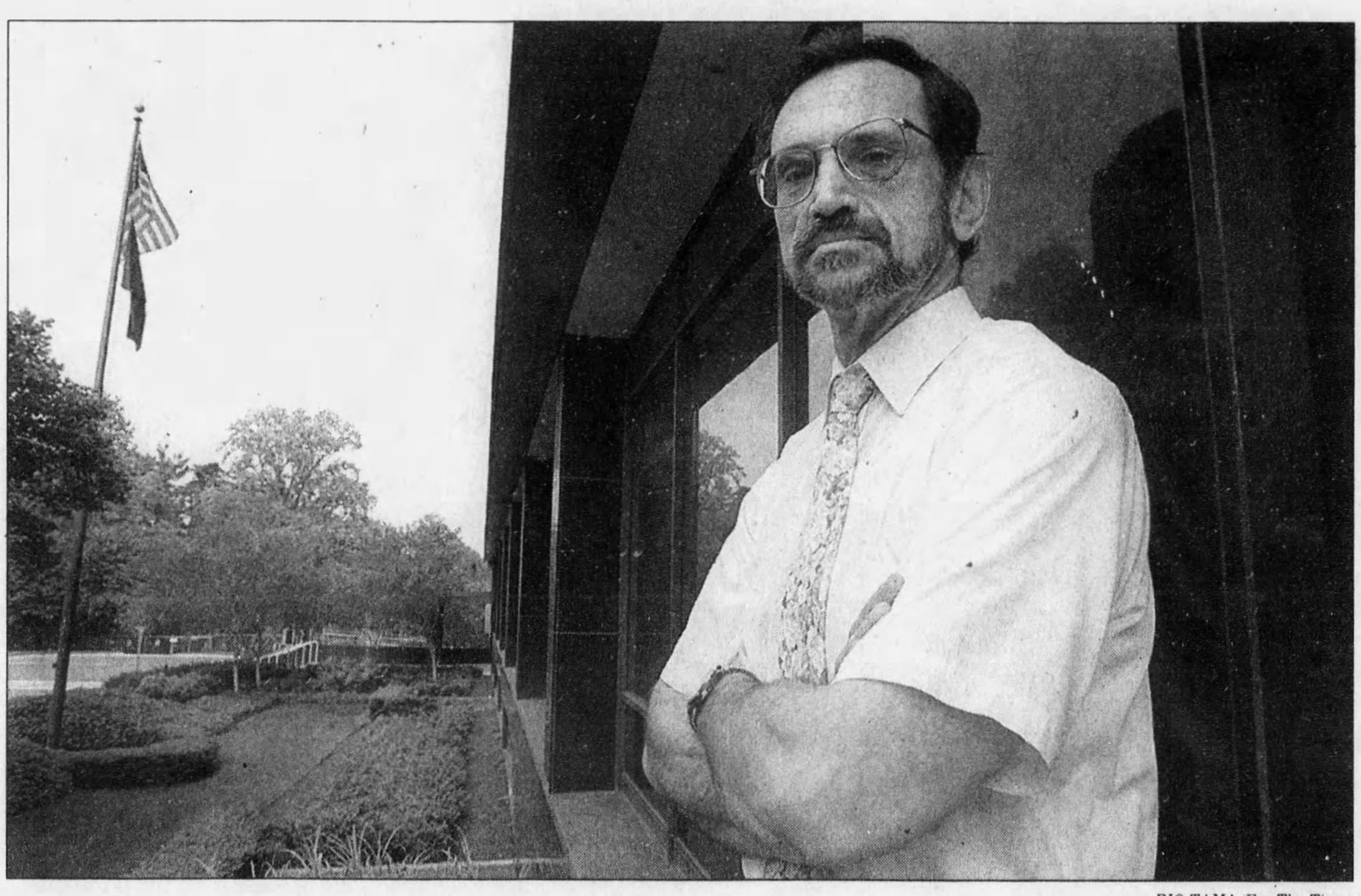
"At the [November 1999] advisory committee, the company proposed that these were [unsurprising] incidences of ischemic colitis, not causally related to drug," Woodcock said, adding: "We can't not approve drugs because they have certain side effects; they're all going to have side effects. We have to determine, are they going to be adequately managed?"

In subsequent written comments, Woodcock noted that some patients complain when a drug they believe helps them is withdrawn.

"People who suffer from serious, life-limiting, or life-threatening illnesses have repeatedly and forcefully told the FDA that they are willing to take greater risks because of the nature of their illnesses," Woodcock told The Times.

A Glaxo executive, Dr. Richard S. Kent, said the company continued to believe that the risks could be satisfactorily managed through labeling and related measures.

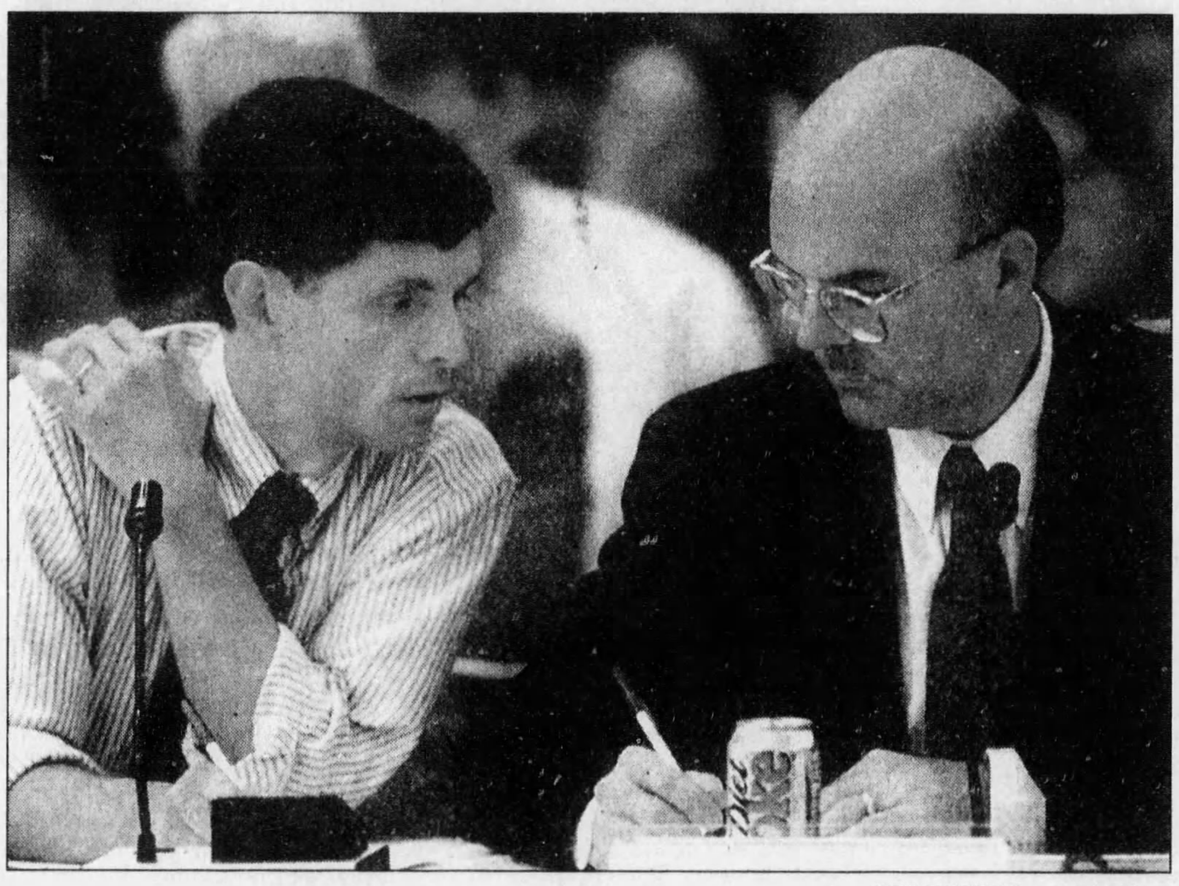
During the nine months that Lotronex was on the U.S. market, sales exceeded $56 million through October, according to the research firm IMS Health. The drug was never sold in any other nation.



RIO TAMA/For The Times

"The death of the patient ... in May 1998 provided strong evidence that Rezulin could not be used safely."

Dr. Robert I. Misbin: The FDA medical officer wrote to the House Energy and Commerce Committee that "the death of the patient ... in [the National Institutes of Health] study in May 1998 provided strong evidence that Rezulin could not be used safely."



JEFF MANKIE/Los Angeles Times

Senior FDA officials Dr. David J. Graham, left, and Dr. Murray M. "Mac" Lumpkin attend a hearing on Rezulin. Graham had warned that Rezulin was among the most dangerous drugs on the U.S. market.

REZULIN

With Each New Fear, a Change to the Label

Diabetes drug left on market a year after being listed among most risky.

Soon after Warner-Lambert Co. submitted the diabetes drug Rezulin for FDA review in the summer of 1996, the medical officer assigned to examine it began finding problems. Dr. John L. Gueriguian cited Rezulin's potential to harm the liver and the heart. He questioned its viability in lowering blood sugar for patients with adult-onset diabetes.

Gueriguian was stripped of the assignment in November 1996 after Warner-Lambert complained that he used intemperate language while discussing the drug. His medical review—recommending against approving Rezulin—was purged from agency files and withheld from an FDA advisory committee.

Officials completed the review of Rezulin within six months and approved it in January 1997. Warner-Lambert's chief executive told investors he foresaw a "billion-dollar blockbuster."

"Seinfeld" actor Wayne Knight was featured in lighthearted TV ads for the flu drug Relenza, which underwhelmed an FDA panel.

By fall 1997, dozens of patients on Rezulin had been hospitalized and a handful of cases of sudden liver failure had been reported to the FDA.

Those first cases prompted the removal of Rezulin from the market in Britain on Dec. 1, 1997—sparking an 18% drop in Warner-Lambert's stock on the New York Stock Exchange. But senior FDA officials stood behind Rezulin by embracing a series of incremental labeling changes.

Two changes came in late 1997 and a third came in July 1998. Each change recommended the monitoring of patients' liver functions as a means of safeguarding against organ failure.

In March 1999, a senior FDA epidemiologist, Dr. David J. Graham, warned that Rezulin was among the most dangerous drugs on the American market. He said that patient monitoring would not protect them from liver failure. Indeed, three patients who were monitored monthly in controlled studies, including one by the National Institutes of Health, suffered liver failure and died.

"The death of the patient ... in [the] NIH study in May 1998 provided strong evidence that Rezulin could not be used safely," Dr. Robert I. Misbin, an FDA medical officer, wrote in a July 3, 2000, letter to the House Energy and Commerce Committee.

Rezulin had not been proved to save lives or to reduce the serious complications of adult-onset diabetes. A fourth label change was implemented in June 1999. But deaths and hospitalizations continued.

The FDA announced on March 21 that Rezulin would be pulled from the market. By that time, the agency had tied 63 liver failure deaths to the drug. Reports filed with the agency through June 30 cited Rezulin as a suspect in a total of 391 deaths.

Officials have never estimated how many Rezulin patients died of heart-related complications. As a condition of approval, the FDA had requested that Warner-Lambert perform a study of the drug's effect in heart-failure patients; the study was never completed.

Before and after the withdrawal, FDA officials overstated Rezulin's scientifically proved benefits. For instance, agency ombudsman James Morrison wrote in June that Rezulin "has been shown to reduce or delay long- term, serious effects of diabetes, including death." Asked the basis for this claim, FDA spokesman Laurence Bachorik said the comments "were not intended as definitive scientific observations."

Six specialists who were involved in Rezulin's approval recently questioned why the drug was given a fast-track review. A "Lessons Learned" report posted in November on the agency's Web site said: "A final major concern of the subjects interviewed ... was the lack of adequate time to review the application."

Woodcock said agency specialists had hoped Rezulin would offer "significant improvement" over the nine or more existing treatments for adult-onset diabetes. As for the decisions that kept Rezulin on the market, Woodcock said she wanted first to see if two newer drugs approved in 1999 were less toxic to the liver. Gueriguian said Rezulin is an example of how senior FDA officials relied on a company's hopes at the expense of public health.

"It really doesn't matter if it was incompetence or dishonesty," he said. "The result is the same: People died unnecessarily."

Rezulin generated sales totaling $2.1 billion for Warner-Lambert in its three years on the U.S. market.

RELENZA

Official Asks If One Day Less of Flu Is Worth It

Still on the market, the drug has been linked to 22 deaths so far.

Glaxo executives were steaming in early 1999 over the work of biostatistician Michael Elashoff and other FDA reviewers who had examined the company's new flu drug, Relenza.

The reviewers found that Relenza was no more effective than a placebo in treating common flu symptoms among American patients. The drug showed better results in foreign studies. But the reviewers also found that Relenza, a powdery inhalant, was potentially unsafe for flu patients with asthma or other respiratory disease.

Relenza is not a vaccine. It is designed to be taken within two days of the onset of flu-like symptoms such as fever, cough, sore throat or headache. Relenza may reduce by about one day a patient's symptoms.

The drug underwhelmed members of the FDA's Antiviral Drugs Advisory Committee. It voted, 13 to 4, on Feb. 24, 1999, to reject it.

"There isn't sufficient efficacy to warrant me recommending this drug for my family or myself," said Dr. John D. Hamilton, a professor of medicine at Duke University. Said another committee member, Dr. Sharilyn Stanley of the Texas Health Department: "I have significant concerns."

Glaxo reacted quickly.

Dr. James Palmer, the company's director of medical, regulatory and product strategy, told an FDA administrator in a March 2, 1999, letter that the staff's position on Relenza "is completely at odds with the will of Congress that drug development and approval proceed swiftly and surely." The letter was addressed to Dr. Heidi M. Jolson, director of the FDA's antiviral drugs division.

The Glaxo executive accused the reviewers of "blindsiding" the company. He said one FDA medical officer "exerted considerable and, we believe, misguided and inappropriate influence on the review." He decried the "total silence" at the advisory meeting of another agency physician. He termed Elashoff's analysis "extreme." He said the "advisory process was distinctly biased against fair and open consideration of [Relenza]." A copy of the letter was obtained by The Times.

Elashoff said his superiors told him he would no longer make presentations to the advisory committee. He said he was asked at least five times to delete the anti-Relenza recommendation from his review. He refused. The FDA declined to comment on these matters.

The agency approved Relenza on July 26, 1999. In a memo dated that same day, Jolson provided a mixed assessment.

Relenza, she said, had not been shown effective for patients over 65 or those "with a variety of respiratory, cardiovascular and other medical conditions." She said "special precautions are warranted" if Relenza is used by patients with respiratory disease. These groups would encompass patients most vulnerable to death from the flu. On the other hand, Jolson said, "the totality of the data" suggested that some Relenza patients could expect modest benefit and that their influenza A or B symptoms might improve an average of one day sooner by taking the drug.

The FDA medical officer first assigned to review Relenza, Dr. Barbara Styrt, wrote that "a rationale can be constructed either for non-approval or for approval." She ultimately backed approval, saying that concerns could be addressed through "label language" and later studies. Analysts at Merrill Lynch & Co. predicted the drug would generate sales topping $400 million within four years.

Glaxo, aiming for customers as widespread as the flu itself, last fall placed ads for Relenza on network television. The lighthearted spots featured an actor from the "Seinfeld" sitcom.

Problems emerged quickly.

Following the voluntarily reported deaths of seven Relenza patients, the FDA issued an unusual "public health advisory" to doctors on Jan. 12, 2000, warning of the limited role of Relenza and another recently approved flu-symptom drug. Two of the dead had bacterial infections and should have been treated with antibiotics.

The agency said it had received "several reports of deterioration of respiratory function following inhalation of Relenza in patients with underlying asthma" or another breathing problem. Reports filed through June show that Relenza was cited as a suspect in 22 deaths.

In July, Glaxo issued a warning letter to health professionals, noting "reports of serious respiratory adverse events when Relenza was used in patients with known airways disease." The letter also said that patients with no history of such disease had suffered "decline in respiratory function."

The company added: "Some adverse events have required immediate treatment or hospitalization, and some patients ... have had fatal outcomes." The Glaxo letter said it was "difficult to determine" whether Relenza caused the deaths.

None of which has surprised Elashoff.

"Even if you accept the company line, that it knocks a day off the flu, a day is not much when you compare it to your life," he said, adding that the approval "was certainly a top-down decision."

Woodcock said the FDA's actions reflect a balancing of risks and benefits. She noted that "strengthened" warning language was added to the product label in April and that a newer study had shown the drug to be effective and safe for children age 7 and older.

Glaxo spokeswoman Ramona DuBose said Relenza "is an important tool for physicians to have to reduce the risk of the disease."

She said the drug can reduce symptoms from both A and B flu strains "by at least a day."

The Glaxo executive wrote the letter in March 1999, DuBose said, to "vehemently protest" the FDA staff's performance at the advisory committee meeting. "We weren't given the opportunity to fully prepare our responses to the FDA's questions."

DuBose said Glaxo would not comment on the volume of reported deaths, adding: "No causal relationship has ever been established between Relenza and any death, anywhere in the world."

THE NEW FDA

An Adult Medicine Is Given to a Girl, and She Pays a Heavy Price

■ Serzone— The FDA didn't endorse use among youths, but knew it was 'likely.' Teen will suffer lifelong effects.

By DAVID WILLMAN
TIMES STAFF WRITER

BRIAN WALSKI/Los Angeles Times

Alissa Robinson, 18, faces a lifetime of uncertain health after nearly dying while taking the antidepressant Serzone. She and her parents, Jimmie and Brenda, struggle to recover from the ordeal while recalling her "puke bucket," a liver transplant and ongoing medical problems.

NORWOOD, Ohio—When a hospital psychiatrist prescribed an antidepressant called Serzone for their 15-year-old daughter, Jimmie and Brenda Robinson assumed it was safe.

The episode in February 1997 haunts them—Alissa Robinson nearly died while taking Serzone. After suffering liver failure and undergoing a transplant, she now faces a lifetime of uncertain health and worry over how she will pay for her care.

Serzone, it turns out, was not intended for children or adolescents, and the label said its safety and effectiveness "have not been established" among the young. However, when FDA officials approved Serzone in December 1994, they suspected its use would not be confined to adults.

"Since it is likely that [Serzone], once marketed, will be used in children and adolescents ... we ask that you commit to conducting, subsequent to approval, studies in these populations in order to provide the safety and efficacy data needed to support such use," wrote an FDA administrator, Dr. Robert J. Temple, in a Nov. 7, 1994, letter to Serzone's manufacturer, Bristol-Myers Squibb Co.

The company agreed to conduct the research, among patients age 7 to 17, and to report the results to the FDA. But nearly six years later, no results have been made public. Doctors may continue to lawfully prescribe it for any purpose they deem appropriate.

A spokeswoman for Bristol-Myers said it hopes to report results to the FDA "in the early part of 2002."

In an interview at the family's home, Brenda Robinson said she was unaware that the FDA had not endorsed Serzone's use in adolescents.

"That comes as a big surprise," Brenda Robinson said. "If it's an adult medicine, why did [the doctors] give it to her?... These drugs should be tested for the people they're going to be used in."

Serzone has been an important drug for Bristol-Myers, generating sales of $1.1 billion through October, according to IMS Health, an information services company. Eighteen cases of liver failure involving Serzone patients were reported to the FDA from 1996 to June 2000. The product labeling was changed, subsequent to Alissa's use of Serzone, to note "rare reports of liver ... failure, in some cases leading to liver transplantion and/or death."

According to an article coauthored by one of Alissa's physicians and published Feb. 16, 1999, in the Annals of Internal Medicine, Serzone was "the most likely cause" of her liver failure.

For now, Alissa and her parents are left to wonder what her life might have been if she had not taken the drug.

Brenda Robinson points to the maroon "puke bucket," Alissa's constant companion in the spring of 1997. By Memorial Day weekend that year, three months after going on Serzone, Alissa was nauseated and vomiting twice or more daily, according to medical records and interviews. Her eyes and skin had yellowed, a sign of jaundice.

When specialists at Children's Hospital Medical Center in Cincinnati admitted Alissa on June 12, they found she was suffering liver failure. Alissa was placed on a waiting list for a transplant. Amid the gantlet of tests and diagnostic procedures, Alissa's flowing, auburn hair was cut, her head shaven.

"That was the worst part," Brenda Robinson recalled. "When she woke up bald ... she went to pieces."

The morning of June 14, Jimmie and Brenda said, one of the doctors told them that Alissa, by then in a coma, could die within days unless a donor organ came available. Brenda, an upbeat woman who works in the auditor's office at the local city hall, lived at her daughter's bedside.

On June 16, Alissa underwent the transplant. "She came this close to dying," Brenda recalled, struggling with her emotions at the memory.

Alissa was reluctant to discuss the difficulties. But when an earlier portrait of her was brought to the family's kitchen table, she said evenly, "That was in my pretty days."

Alissa's father worries that no employer will offer her health insurance, that she will unable to pay for essential prescriptions and care. Just in the last year, Alissa was twice hospitalized: Three days because of a bug bite that became infected; more recently for surgery to repair a rupture in her transplant incision.

"It's destroyed her for life; it's destroyed us," said Jimmie Robinson, a machinist in this blue-collar suburb of Cincinnati.

The family is suing Bristol-Myers in state court, alleging that Serzone is a defective product and "unreasonably dangerous."

The company declined to comment on the litigation. Other named defendants include Good Samaritan Hospital of Cincinnati and two doctors, including the psychiatrist who prescribed Serzone to Alissa. All of the defendants are contesting the lawsuit.

An FDA spokesman, Jason Brodsky, said the agency has within the last three years "issued a formal written request to Bristol-Myers Squibb to study [Serzone] for the treatment of depression in children ages 7 to 17."

A Once-Scorned Drug Gets a New Chance

■ Thalidomide—Approved to treat just leprosy, its alleged promotion as treatment for cancer draws sharp criticism.

By DAVID WILLMAN
TIMES STAFF WRITER

WASHINGTON—On Sept. 5, 1997, a Food and Drug Administration panel met to ponder the once-imponderable: Should thalidomide be approved in the United States?

Decades earlier, the pill's use abroad as a nighttime sedative by expectant mothers had resulted in the gruesome disfiguring of thousands of newborns. The FDA medical officer responsible for keeping thalidomide off the U.S. market, Dr. Frances O. Kelsey, was honored as a national hero in 1962 by President Kennedy.

Thirty-five years later, the Celgene Corp. was seeking FDA approval of thalidomide, ostensibly for an extremely narrow use: treating the complications of leprosy.

The agency already allowed experimental use of the drug for leprosy and AIDS, and some of these patients saw improvements in skin growths or sores. But the drug's effectiveness remained unproven. A study published by the New England Journal of Medicine in May 1997 found that some AIDS patients' underlying disease worsened on thalidomide, compared with those who took a placebo.

Unlike at most advisory meetings, the top administrators at the FDA's drug-review center—Dr. Janet Woodcock and her deputy, Dr. Murray M. "Mac" Lumpkin, took seats at the U-shaped conference table. Agency administrators had encouraged Celgene in 1995 to test thalidomide's potential, following interest and illicit distribution of the drug among AIDS patients.

None of the three FDA medical officers who reviewed thalidomide supported approval. Drs. Kathryn O'Connell and Brenda Vaughan and their boss, Dr. Jonathan Wilkin, found that the studies submitted by Celgene failed to establish effectiveness or safety.

Wilkin, director of the dermatology drugs division, worried that Celgene would seek a far broader market for thalidomide. Once a company wins approval for a new drug, the compound may be prescribed lawfully for any medical purpose.

"If there are two dozen new patients a year that are going to be using thalidomide for [leprosy], then that hardly seems to me to be a profitable market," Wilkin told the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee. "So, the question is where is this really leading? I think that off-label use is where the vast majority of the use would occur. It would dwarf actually the use for" leprosy.

Wilkin decried the absence of any scientifically acceptable study supporting Celgene's application. He warned of the drug's capacity to severely damage white blood cells and the central nervous system, including among AIDS patients. Wilkin flatly told the advisory committee that thalidomide was "not approvable."

Just as Wilkin finished speaking, Lumpkin raised his left hand to be recognized.

"I just don't want there to be any misunderstanding within the public that what you've heard is, quote unquote, the agency's recommendation," he said, adding: "What the primary reviewer, what the secondary reviewer, what the division director have done is given us their opinions and that's part of the equation.... They are not the deciding officials."

The advisory committee voted 8 to 1 that the benefits of thalidomide outweighed the risks. On July 16, 1998, the agency approved thalidomide, declaring it "will be among the most tightly restricted drugs ever marketed."

At Celgene, the top executive credited Woodcock and Lumpkin for trumping the presentations of division director Wilkin, and medical officers O'Connell and Vaughan.

"Certainly there was a lot of concern on our part that in the end the FDA would decide not to approve thalidomide based on some of those presentations," said John W. Jackson, company chairman and chief executive officer. "However, we were confident that the senior people at the FDA had encouraged us.... They felt that it should get approved and be on the market."

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Jackson added: "They felt ... there was a need for this drug in the AIDS community."

Celgene from the outset promoted thalidomide for purposes having nothing to do with leprosy, including the treatment of various cancers, officials later alleged. On July 30, 1998—just two weeks after thalidomide had been approved—officials working in the FDA's drug-marketing office contacted Celgene and expressed concern about the company's promotion of thalidomide for uses "other than" the narrow, approved treatment of leprosy.

On April 21, 2000, the director of the marketing office, Thomas W. Abrams, wrote to Celgene's Jackson, alleging that the company "is demonstrating a continuing pattern and practice of violative behavior." Abrams added: "Celgene's actions are particularly troublesome.... Perhaps more than for any other available drug, the need to provide and distribute thalidomide responsibly is essential to the public health."

Jackson said in an interview that Celgene "has never advocated any off-label promotion [for thalidomide]. Our objective was and always has been to comply fully with the rules and regulations of the FDA."

After the FDA's approval of thalidomide, the drug gained virtually no popularity in treating AIDS patients. Jackson said that thalidomide is now being used "almost entirely" for treating various cancers.

Reports filed with the FDA since the drug's approval cited thalidomide as a suspect in 16 deaths from the July 1998 approval through June 2000. Three of those who died, women ages 56, 59 and 63, had a white blood cell disorder, neutropenia, about which Wilkin had warned the advisory committee.

Jackson said the deaths were unsurprising because thalidomide is used to treat extremely sick patients. He said that special controls for dispensing the drug have proven a success and that no birth defects have emerged. Doctors and pharmacies must register with Celgene before dispensing thalidomide, and each new patient is supposed to view a video, showing the flipper-like limbs that can result from use during pregnancy.

Agency officials declined to allow Wilkin, O'Connell or Vaughan to grant interviews for this article. The FDA also has declined for more than a year to provide their medical reviews, requested under the Freedom of Information Act.

Said a specialist familiar with those documents, who spoke on condition of anonymity: "The reviewers looked at the data set, considered the public health and did what they thought best.... If you're looking for differences between upper management and the reviewers—read the reviews."

An FDA spokeswoman, Rae Jones, said the prospect of off-label use "had no bearing" on the agency's decision to approve thalidomide.

When thalidomide was approved, securities analysts predicted that it could generate annual sales of $300 million by 2004.

How Deaths Were Calculated

Reports of adverse drug reactions to the Food and Drug Administration are considered by public health officials to be the most reliable early warnings of a product's danger. The reports are filed to the FDA by health professionals, consumers and drug manufacturers. The Los Angeles Times inspected all reports filed in connection with seven drugs that were approved and withdrawn since 1993. By hand and by computer, The Times counted 1,002 deaths in which the filer identified the drug as the leading suspect. Since fall 1997, this top category has been termed "primary suspect." The Times did not count any deaths in which the drug was identified as the "secondary suspect" or less. The methodology and results were reviewed by Sheila R. Weiss, a former FDA epidemiologist who is an assistant professor at the University of Maryland's department of pharmacy practices and sciences.