Speedier FDA Drug Reviews Are Fertile Ground For Hype (Part 1)
By Otesa Middleton
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WASHINGTON -(Dow Jones)- In the spring of 1987, Oscar-nominated writer Larry Kramer and 16 enthusiastic comrades lay down on Broadway to jam rush-hour traffic on one of Manhattan 's most popular streets.

Their target: the Food and Drug Administration. Their message: approve AIDS drugs - now!

Kramer's patient-activist group, ACT UP, and the ensuing swirl of nationwide AIDS protests succeeded. The FDA bowed to activists' pressure and devised ways to review drug applications in record time.

It also forced the agency to rethink and revamp the way it deals with drugs that meet unmet needs. FDA cut the time it spent reviewing applications for these lifesaving drugs to six months.

More than a dozen years after Kramer's protests, some upstart drug makers are cashing in on the fast track procedures in ways the AIDS activists did not envision.

ImClone Systems Inc. (IMCL), Cell Pathways Inc. (CLPA) and others parlayed speedy drug designations by the FDA into press coverage for experimental products, attracting millions of dollars of investment in the process.

Before AIDS revolutionized drug approvals, the FDA sometimes waited years before even starting its time-consuming drug application review, a process that involved meticulously reading hundreds of books full of scientific documents. Today, companies proudly announce if a product qualifies for a special six-month review, a rarity before AIDS.

FDA Designation Can Be Abused

Although approval still isn't guaranteed, such a designation carries cachet, a tacit endorsement that the nation's health arm considers a drug an important advance. The designation can also fuel hype over unapproved drugs.

"Companies like ImClone and Cell Pathways have chosen to use these designations by the agency as promotional techniques to generate interest and perhaps investment in their companies," said Ira Loss, a pharmaceutical analyst at Washington Analysis who has followed the FDA for 25 years.

"ImClone did great press releases and not very good clinical work," he said. "ImClone failed to communicate accurately with the public."

Consider the case of ImClone's experimental colon cancer drug, Erbitux.

FDA deemed the drug a fast-track product in February 2001. ImClone capitalized on the designation, throwing promotional events such as a Doobie Brothers concert at a major international cancer meeting in San Francisco in May 2001.

By September 2001, ImClone managed to woo Bristol-Myers Squibb Co. (BMY) into investing as much as $2 billion for a stake in the company plus a 40% share of the expected profits of the experimental cancer drug.

Investors cheered; ImClone shares rose 13% to $56.60 on Sept. 19, when the pact was disclosed.

The party ended in December when the FDA threw out the Erbitux application, citing missing information and incomplete test results. ImClone's stock tanked; since the fall of 2001, investors have lost about $6 billion.

The FDA cited several problems. Instead of being tested by itself, Erbitux was given to patients in combination with Pharmacia Corp.'s (PHA) chemotherapy Camptosar, which has been on the market for six years, said Dr. Richard Pazdur, FDA's director of cancer drugs.

Pazdur told a U.S. House panel in June that regulators said they couldn't tell which drug caused the benefits or the side effects. He called Erbitux a promising drug that ran into problems because of "sloppiness."

"It's called good drug, bad development," Dr. Pazdur testified.

The aftermath still is being felt.

In June, ImClone's former chief and founder, Samuel Waksal, was arrested on insider trading charges. Waksal's friend, home decorating maven Martha Stewart, sold nearly 4,000 ImClone shares the day before the adverse FDA ruling. Congress wants the Justice Department to investigate.

Bristol-Myers restructured its deal that originally involved paying ImClone $1 billion for clearing certain regulatory hurdles in the drug's approval.

ImClone officials didn't return calls requesting comment for this story.

The Saga Of Cell Pathways' Aptosyn

In late 1998, FDA named Cell Pathways' Aptosyn a fast-track drug to treat a pre-cancerous colon disorder. A year later, Pharmacia Corp.'s (PHA) blockbuster arthritis painkiller Celebrex became the first drug approved for the colon ailment, taking the pressure off FDA to get something on the market.

In February 2000 Cell Pathways' stock traded as high as $66 as eager investors scooped up shares on the company's assurances Aptosyn would win FDA approval by that August. "We are very encouraged by all our results to date with Aptosyn as a potential new treatment," Rifat Pamukcu, the company's chief scientific officer, said in a May 23, 2000 press release. Earlier that year, it issued other upbeat press releases, such as one titled, "Aptosyn Commercialization Remains on Track."

In September 2000, Cell Pathways announced the FDA turned down the company's application. The company's shares lost more than two-thirds of their value, plummeting below $10.

Cell Pathways in February 2002 settled a shareholder suit alleging the company hyped the stock while submitting inadequate data to the FDA. The lawsuit charged Aptosyn reduced formation of colon polyps

when patients had polyps surgically removed before the study. To settle the case, Cell Pathways paid 1.7 million shares of common stock and $2 million, which its insurer would reimburse the company.

Cell Pathways spokeswoman Joan Kureczka said the company "put out a brief press release" when Aptosyn was named a fast-track drug.

Kureczka said treating rare colon polyps is no longer "the primary thrust" of the Aptosyn development program, which instead is looking at treating other cancers. Currently, the company's stock sells for about $1.

FDA Doesn't Monitor Wall Street

FDA, charged with protecting the public health, doesn't always object when companies aggressively use the agency's designations to land financial backing for unapproved and unavailable drugs.

"Getting into economic consequences is so at odds with our current responsibility. It's not what you want a regulatory agency to do," said Dr. Robert Temple, a top official in FDA's drug center. "Monitoring what goes out to Wall Street is not considered part of our arena."

FDA sends letters advising companies against promoting unapproved products. But the agency doesn't crack down vigorously if the drug isn't on the market because the overzealous statements don't directly harm patients.

"Sometimes we act, but it is more difficult because no one can get the drug," Temple said.

The FDA's office of advertising and communications will reprimand companies with a letter if they flagrantly hype an unapproved drug.

"If they are misleading, we feel perfectly comfortable going after them," Temple said. "If they put out promotions that are false or misleading we would tell them to stop or direct it to the SEC," or the Securities and Exchange Commission.

Critic Cites 'Huge Marketing Spin'

One FDA critic said while the agency needed to improve its handling of treatments for deadly diseases, now there is too much emphasis on speedy drug reviews.

Drug companies are capitalizing as a result, said Dr. Sidney Wolfe, who founded the consumer group Public Citizen with Ralph Nader some three decades ago.

"There is no question there is a huge marketing spin that begins as soon as a drug gets fast-track designation -the expectations are greater," said Wolfe.

FDA needs more authority and staff to be able to screen companies' statements and fine drug makers if they are promoting unapproved products, Wolfe said.

"FDA should care about it," Wolfe said. "The FDA has not been properly tough on that aspect. "

Loss, the veteran FDA analyst, sides with the FDA view that it lacks staff - and mission - to review potentially misleading statements about new drugs. "It's not realistic," Loss said. Such reviews are the purview of the SEC, he said.

Hemant Shah, an independent pharmaceutical analyst at HKS & Co., said companies will try to generate investment interest by telling industry analysts "this has the potential to become a big drug."

At the same time, AIDS activists such as Kramer want the FDA to continue to move swiftly to get lifesaving products on the market. However, Kramer objects when companies manipulate the system to gin up investor interest.

"Drug companies need money, but there's got to be a way of balancing the two," he said.

-By Otesa Middleton, Dow Jones Newswires

AIDS Crisis Revolutionized FDA Drug Approvals (Part 2)
By Otesa Middleton
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WASHINGTON -(Dow Jones)- Larry Kramer recalled how friends were "dying like flies" in the 1980s when he started his successful crusade to speed Food and Drug Administration approval of lifesaving drugs.

To get the agency's attention, Kramer and his allies hanged an FDA chief in effigy, hurled blood on FDA's headquarters, and dumped coffins on the White House lawn.

He formed the AIDS activist group ACT UP, which pressed the FDA to shorten time for drug reviews by using computers instead of relying on rooms full of binders. They also wanted the FDA to work with companies earlier to develop better trials.

As AIDS steadily devastated the immune systems and killed thousands of young gay men, Kramer pressed his cause with greater urgency.

"For everybody else, it was peace time," Kramer said, while for the gay community, it "was war time." The slow-moving agency was "protecting us to death."

ACT UP's demonstrations put the spotlight on the agency charged with shielding America from unsafe drugs - and forced the agency to speed reviews of potentially lifesaving medicine.

The changes are still being felt today.

"The real impetus to the culture change in the mindset of the FDA happened because of the AIDS crisis," said Dr. Murray Lumpkin, one of the agency's top officials who is in charge of FDA's dealings with foreign drug regulators.

Little Ammunition To Fight AIDS War

About the time Kramer was hurling blood on the FDA's building, Lumpkin was inside, adjusting to his new job, and a huge challenge: running the anti-infective division at the peak of the AIDS learning curve.

AZT, or Retrovir, the first drug approved to treat the virus, had only been on the market two years when Lumpkin joined FDA in 1989. Just five years earlier scientists began blaming HIV for causing AIDS and the first blood test for the virus hit the market in 1985.

Lumpkin's division had little ammunition to fight a war already responsible for taking more than 60,000 lives. His group of 66 workers used just two computers and no fax machine.

For each application, reviewers scoured at least 500 volumes of data, each two- to three-inches thick.

"They'd be delivered on the back of an 18-wheeler and stack up against the wall," Lumpkin said. "We didn't have space to put them all."

After reading millions of pages of chemical, pharmacological, statistical, biological and manufacturing data, reviewers jotted down reports on yellow legal pads before passing the work over to a secretary to type.

"And people wondered why it took four-and-a-half to five years to review a drug," Lumpkin said. "FDA had no financial resources to buy computers."

"Time was lost," Lumpkin said. "Applications would sit in queue half of that time."

Congress Moves To Speed Drug Approvals

In 1992, Congress passed the Prescription Drugs User Fee Act, commonly called PDUFA, which required companies to pay a fee for FDA review of new drug applications.

"It gave us the financial resources to put a computer on everyone's desk," said Lumpkin. The next year, he moved up to deputy director of FDA's drug center, in charge of implementing the program.

Instead of arriving via big rig, today most new drug submissions arrive on CD-ROM.

By paying FDA, drug makers get a guarantee their applications will be reviewed within 10 months for run-of-the-mill drugs. If the FDA deems the drug a breakthrough to treat a deadly disease, it will review it within six months.

With a fast-track label, FDA guides the company through the review process and allows the drug maker to submit its application in sections on a rolling basis.

A priority designation, which most fast-track products also receive, then assures the quicker six-month turnaround. Both priority and fast-track are reserved for drugs that address life-threatening ailments and fill an "unmet medical need," according to FDA's guidelines.

Drugs can win conditional approval through the FDA's accelerated approval process by meeting a surrogate endpoint, or pre-established goal other than saving lives or curing the disease. After the drug is on the market, the manufacturer must finish the required studies and apply for full approval.

Here's an example. Since the AIDS virus can incubate in the body for a decade or more, a trial to prove a drug helps people with AIDS live longer would take more than 10 years to complete. Using a surrogate endpoint, treatments can be approved by demonstrating the medicine increases immune system cells. In cancer trials, a common surrogate endpoint is tumor shrinkage.

Prior to the emergence of AIDS, FDA categorized drugs as A, B or C. Brand-new drugs for life-threatening diseases received an "A" designation and more attention. However, this didn't guarantee a speedier review. Because AIDS was a new, deadly and communicable disease, the agency created a new category: "AA." Later it revamped the entire review system.

Drug Approval Permanently Altered

Kramer said the aggressive style of his group, coupled with the heinous nature of AIDS, altered drug approvals in the U.S.

"It's the biggest success," Kramer said. "This is so beneficial for every illness."

Last month, Kramer went up to the microphone as a public speaker at an FDA advisory panel meeting on a hepatitis B drug. Last year, Kramer, who is now 67, became the oldest person infected with both HIV and hepatitis B to receive a liver transplant. At the FDA meeting, he laughed that this is the first time he was welcomed at one of the FDA's meetings.

"When we first went to the meetings, they wouldn't let us in," Kramer said. "They'd call the cops."

-By Otesa Middleton, Dow Jones Newswires

FDA Says Drug Approval Not Harder, Just Slower, Part One of a Two-Part Series
By **Otesa** Middleton
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WASHINGTON -(Dow Jones)- Is the Food and Drug Administration getting tougher?

Recently, a few high-profile negative votes by the FDA's panels have caused some to contend the agency and its advisors have gotten tougher.

The FDA asks the panels to meet to discuss tough issues. The panels consist of outside experts. Their discussions provide a public forum to consider tough situations such as whether a drug should be approved, whether a drug already on the market should be recalled or whether a drug is safe for children.

The issue of whether panels have become tougher follows high-profile recalls and criticism that the agency allowed unsafe products on the market without ample testing.

The agency, according to a spokesman, doesn't have statistics on the proportion of positive and negative committee votes, so it's not possible to say whether standards are higher than they were before.

FDA: No Tough-Guy Stance

Dr. Janet Woodcock, who heads the FDA's drug division, said neither the FDA nor its 32 committees that review applications for new drugs have been ordered to get tougher.

There are, however, fewer meetings scheduled for this year. In 1988, there were 20 meetings. The number soared to 51 meetings in 1995, but has since dropped to 32 scheduled meetings for this year. Some meetings last more than one day and review more than one product. The committees' comments and votes weigh heavily on whether the FDA will allow a product on the market, although the agency sometimes rejects the advice of its committees.

"We don't think there's been any overall trend," Woodcock said. "People look at high-profile turn-downs and think they discern a trend."

"We try to aim for consistency of review, and we don't believe there is a shift in the standard," Woodcock told Dow Jones. "We believe we have to have the same high standard. We haven't changed our definitions for 12 or 13 years."

Watchdog Points to Missteps

Dr. Sidney Wolfe, who runs the health segment of the Ralph Nader-founded consumer group Public Citizen, disagrees.

"The whole FDA drug review process is in a state of turmoil very much related to a series of drug disasters," Wolfe said.

The agency approved 543 new drugs between 1981 and 2000, pulling 14 off the market during that span. Some of the recalled products were big sellers before they were snatched from the shelves. Recalled products include American Home Products Corp.'s (AHP) portion of the diet drug combination fen-phen, which was linked to heart valve damage; Warner-Lambert's **diabetes** drug Rezulin, which was linked to

more than 60 liver-related deaths; and Johnson & Johnson's (JNJ) heartburn drug Propulsid, which was tied to 80 heart-related deaths.

Wolfe said that while the withdrawals have prompted the FDA ands its advisory committees to be more cautious, the caution still hasn't been enough. Citing a Public Citizen study in which some FDA medical reviewers said they felt pressure to approve products they considered unsafe, Wolfe said the FDA review process remains slanted toward drug makers. Also, he said, the agency needs to exclude more advisers from participating in meetings if they have any interest in the product or company. Although committee members are supposed to disclose any such involvement, Wolfe said, "the process needs to be cleaned up."

Neil Sweig, pharmaceutical analyst at Ryan Beck & Co., also said the FDA has had to take a tougher stance because of the recalls.

"If the panels see something wrong with safety and efficacy, they are going after it faster and deeper than previously in this more stringent review period at the FDA," Sweig said.

Advisory Panels—Separate but Equal

But Sweig said because panels deal with specific types of medical products, it's difficult to say there's a movement afoot.

"Each advisory group has a different therapeutic area and is a kingdom unto itself," Sweig said. "Some are easier to get along with than others. Some areas are far more difficult."

FDA panels have chairmen, who set the tone, and each division of the agency has a director to send down directives. Sweig, though, said without a captain to lead the entire agency, there is confusion.

"Without a chief executive that all of these other chiefs report to, there is endless chaos," said Sweig, commenting on the lack of a permanent FDA commissioner.

The FDA does acknowledge it's taking longer to get drugs on the market. After rapidly decreasing its approval time from more than 22 months in 1992 to less than a year in 1999, last year the median approval time was almost 16 months.

The FDA's Woodcock said this is because the agency didn't receive as many priority review applications that must be reviewed in six months, thus increasing the average review time because the shorter reviews weren't averaged in.

Also when the agency tells a company to get more data on a drug, that holds up the process, she said.

"Some of the drugs may have been turned down earlier, or we asked for more data," Woodcock said. "A lot of drugs approved in 2000 were submitted a long time ago."

The advisory committees, Woodcock said, are a forum for the FDA to bring scientific questions to external experts to get a broad range of opinions.

"We don't bring things that are slam dunks before the panel," Woodcock said. "We bring real questions."

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Part II: FDA Says Drug Approval Not Harder, Just Slower

WASHINGTON (Dow Jones)--For the past four years, between teaching classes, running a heart failure center and seeing patients, Dr. Milton Packer has periodically trekked from New York to Washington to tell the government what it should do about heart and kidney drugs.

One of hundreds of outside experts deputized by the Food and Drug Administration to weigh in on complex matters, Packer was chairman of the FDA's Cardiovascular and Renal Drugs Advisory Committee until the end of June.

Packer, who heads the Division of Circulatory Physiology at Columbia University's College of Physicians and Surgeons, also did a stint on the same panel in the late 1980s.

"It's a positive experience," Packer said. "It's always appropriate for membership to rotate and for others to be given such an opportunity. Now I'm taking a well-deserved break."

Packer sat on one of the FDA's 18 drug advisory committees. In the entire agency there are 32 such groups that give advice to the FDA about drugs, vaccines, devices and other medical products, with some having sub-panels that discuss specific types of medical products.

For more than half a century the agency has coupled its internal knowledge with that of outside experts. This practice was codified when Congress passed the 1972 Federal Advisory Committee Act, outlining how outside advisers should be recruited and used. Consumer representatives were added to panels in the mid-1970s, and committees have since consisted of world-renowned experts plus a public representative.

Ten to 15 advisers sit on each panel, which may consist of the consumer representative, professors, physicians, statisticians, pharmacists, nurses, researchers and chemists.

The FDA may ask the groups if a product should be sold in the U.S., if there were enough people included in a particular clinical trial or if a side effect warrants merely a mention or the agency's most-severe black-box warning. Sometimes a drug already on the market is being considered for approval for a different use. In other cases, unexpected side effects may have popped up and the group must consider whether the drug should be taken off the market.

Although the committees' comments and votes carry a lot of weight with the agency, the FDA has gone against the advice of its advisers on occasion.

Comparing his two terms on the cardiovascular and renal drugs panel, Packer said "the general nature of the questions the FDA asks are the same."

What has changed is the intricacy of the issues.

Trial designs are more complex, which makes analyzing the outcomes more involved.

"The details are more complicated," Packer said. "Because the data is more sophisticated."

John Treacy, who has been the FDA's director of advisers and consultants staff for a decade, said about a third of advisers rotate off the panels each year so the agency is constantly looking for new members.

"It's a little complicated," Treacy said. "We're required to make the committee look like America with a balance of women and minorities, plus we're looking for specific expertise."

For example, Treacy said, if the osteoporosis expert's appointment ends, the agency then looks for another osteoporosis expert to fill the vacancy.

In his 10 years working with the committees he has seen the groups become more diverse.

In 1988, only six of the then 14 drug committees had minority members, that number has increased because "our whole society is changing," Treacy said.

"The Federal Advisory Committee Act requires fair balance based on geography, minority status and gender," Treacy said.

Advisory committees are also getting more attention now, Treacy said.

"Ten years ago one company started videotaping meetings," Treacy said. "Now there are three different firms selling videotapes of meetings."

"There are also more public participants asking to speak at the open public hearings during the meetings," Treacy said. Each meeting sets aside time for any interested party to speak on the issue at hand.

"The public wants to get more involved in the health-care decisions."

However, he doesn't see any change in the attitude of panelists when it comes to voting on drugs.

"Each panel outcome varies tremendously based on the individual results of the clinical trial," Treacy said. "There is no drug out there that is 100% effective or 100% safe and we have to balance the benefits with the side effects."

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