Cetus's Costly Stumble on IL-2

The failure to win approval for Proleukin sent shock waves through the industry, put Cetus's stock in a tailspin, and raised doubts about interleukin-2 therapy

TWO MONTHS AGO, CETUS, one of the most scientifically successful of the nation's biotechnology companies, met face-to-face with the Food and Drug Administration (FDA). In a public forum crammed with stockbrokers and industry analysts, Cetus argued its case for marketing interleukin-2 for patients suffering from renal cell carcinoma, a more-or-less untreatable cancer of the kidney.

In the world of biotechnology, it was a signal meeting. First, interleukin-2 (IL-2) represents a class of agents—biological response modifiers—that are seen as the most important drugs on the horizon for pharmaceutical biotechnology. FDA is anticipating a surge of applications to market these agents—which include the interferons, tumor necrosis factor, and a class of hormones known as colony-stimulating factors. Second, the Cetus application was handled by a new regulatory apparatus. Because FDA has little experience in dealing with biological response modifiers it recently established an advisory committee to help it evaluate these agents and it is channeling applications through a new entity—the Center for Biologics Evaluation and Research—that is separate from the agency's divisions for handling more traditional drugs.

Thus Cetus and FDA were entering uncharted waters. How would each behave? How would they interact? If all went well, analysts were prepared to predict smooth sailing for other companies in the biological response modifiers business.

In addition, Cetus had a special financial stake in winning approval for IL-2, which the company calls Proleukin. As Katherine A. Russell, Cetus's senior vice president for corporate affairs, told the *Washington Post* in an interview before the FDA meeting, "We're reporting losses currently. We're depending on this drug to get more revenues into the company." Cetus posted a net loss of $60 million last year, and its investment in IL-2 alone is estimated to be in the $120-million range. It was reportedly hoping that the FDA would give IL-2 favored status because it is a drug for people who have no other hope. But Cetus blew it.

In oral presentations, the company made claims for IL-2 that went beyond what the data can support. To bolster its case that IL-2 significantly prolongs the lives of kidney cancer patients, it also presented the advisory committee with information that had been marshalled only days before, though the data themselves had been available for some time.

The advisory committee did what advisory committees predictably do in such cases: it pleaded for time to scrutinize data it got that afternoon for the first time and recommended that the company go back to the drawing board to reconstruct all pertinent information in a form better suited to showing the risks and benefits of IL-2.

Product	Company	Recommendation
Interferon-gamma (For chronic granulomatous disease—an inherited immune disorder)	Genentech	Approve
Interferon-alpha (For non-A, non-B hepatitis)	Schering-Plough	Approve
Granulocyte macrophage-colony stimulating factor—GM-CSF (For bone marrow transplant patients)	Immunex	Minor adjustments to application
Interleukin-2 (For kidney cancer)	Cetus	Major revisions and data reorganization

It is worth noting that the interferons have previously been approved for other medical indications.

Split decisions. *FDA's new committee on biological response modifiers approved two applications out of the four it reviewed.*

As Cetus's petition to put IL-2 on the market fell flat, so did its stock. When IL-2 made the cover of *Newsweek* in 1986, Cetus shares were selling at $40. They dropped to $13 the day after the meeting and continued on a rapid downward slide to $8.75.

Cetus's president, Robert Fildes, a businessman who reportedly had been feuding with board chairman and founder Ronald Cape, a scientist, was blamed for the company's poor scientific performance and was forced to resign. The company is regrouping, with Cape temporarily at the administrative helm. At present, Cetus officials are adopting a low profile, in the face of speculation that parts of the company may be sold off. Cetus, for instance, has the patent on PCR or polymerase chain reaction technology for DNA analysis. As one industry CEO told *Science*, "Their PCR business could be sold for millions. So could their operation that manufactures generic anticancer drugs. I'm watching to see not whether Cetus will be broken up but when." Cetus declined to be interviewed on this or other points.

Why did the Cetus case seem so important? The biotechnology industry is unlike many others, financial analysts say, because what befalls one prominent company often affects the way Wall Street sees them all. Some stockbrokers have even warned their customers to stay away from all biotechnology companies.

G. Steven Burrill is a market analyst in the San Francisco office of Ernst & Young. "What happened to Cetus during that FDA hearing is something that all biotech CEOs should think about," he told *Science*. Burrill, who has recently completed a survey of biotechnology companies, notes that there is an unusual link between the financial markets and expectations. "These companies are selling a scientific promise," he says. If the FDA is perceived as a "major barrier to industry," financing will dry up across the board.

Some observers think the psychology of the case is playing too dominant a role in retrospective analyses, however. The Cetus episode may simply be an example of a single company that failed to present its case properly, a couple of them told *Science*. Certainly, what happened to Cetus at the advisory committee meeting indicates no inherent regulatory bias against biological response modifiers, for the same neophyte advisory committee that said "No" to Cetus said "Yes" to two other companies and gave a tentative "Yes"—pending some fine-tuning of the application, to a third (see chart).

How did such a scientifically savvy company stumble so badly? And where does the company's setback leave IL-2 as a possible cancer therapy?

The FDA advisory committee meeting that so shook Cetus was a 1-day performance of a play that had been in rehearsal for more than a year. Cetus's application to market IL-2 was first submitted to FDA in November 1988. During the past year and a half, Cetus and FDA scientists logged hundreds of hours of telephone and fax time, discussing the IL-2 data and data on IL-2 used in combination with LAK (lymphokine-activated killer) cells.

The phone calls and faxes continued right up to the last minute. Jay Siegel, the FDA physician/scientist who has been working with Cetus on the application, told the advisory committee that "Over the past 2 months large amounts of additional data and data analysis regarding these patients have been communicated to the FDA by Cetus on a nearly daily basis up to, and including, last Friday, July 27."

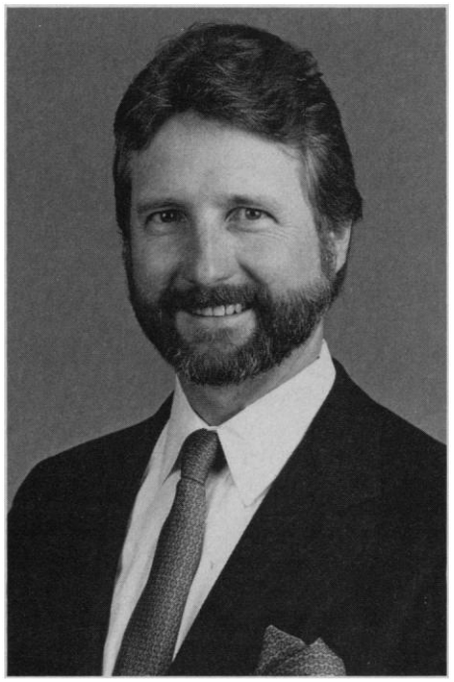
However, it soon became apparent that if there is anything guaranteed to make a group of academics postpone a decision it is last minute data.

The heart of the argument in favor of IL-2 is that when it works, it works spectacularly. Steven A. Rosenberg of the National Cancer Institute (NCI), a pioneer in IL-2 therapy, has achieved the most positive results, FDA says. Three of 42 Rosenberg patients in one series appeared to be cured. A small number of others have gone into partial remission.

According to oncologist Peter Wiernik of the Albert Einstein Medical College in New York, when data are added up from IL-2 studies that NCI is sponsoring at several medical centers nationwide, the combined "complete response rate and partial response rate" is around 18 to 20%. "I have a CV full of papers on renal cell [kidney] carcinoma and I've never seen anything like the response rate we get with IL-2," says Wiernik, who testified for Cetus, and volunteers that he owns no Cetus stock.

But the flip side of these studies is that IL-2 is not effective in a great majority of the cases in which it is used. Moreover, in *all* cases, IL-2 is a highly toxic agent that leads to massive fluid retention, chills, fever, and, sometimes, cardiac failure. Depending upon whom you ask, experts place the mortality rate at 1 to 2%, to 4%.

Advisory committee member Paula Pitha, a cytokine biologist at the Johns Hopkins Hospital in Baltimore, told *Science* that in widespread use, IL-2's toxicity might become a greater hazard. If IL-2 were on the market, "you could impose a great risk on many patients," Pitha says. "It may be fine in Steve Rosenberg's hands where he has a good staff to treat the side effects, or here at Hopkins or other big places. But what about little hospitals? If this drug were widely used, we could see drug-related mortality go way up." Estimates of the number of patients who are diagnosed with kidney cancer each year range from 18,000 to 24,000.



Take-home lesson. *"What happened to Cetus . . . is something that all biotech CEO's should think about," says Steven Burrill.*

Michael Hawkins of NCI, another advisory committee member, is more sanguine about IL-2 toxicity. "Most physicians could learn to use it if they had the cooperation of their intensive care unit people," he says. But Hawkins, who says he would choose IL-2 if he had renal cell carcinoma, thinks that Cetus's application was "premature."

One troublesome problem in sorting out the IL-2 data is that there have been many studies in which the drug is administered in combination with something else. Most prominent among the combinations is IL-2 and LAK.

In defense of its IL-2 application, Cetus presented considerable data on patients treated with IL-2/LAK—data that support a role for IL-2 in kidney cancer. According to people familiar with Cetus, the company believed FDA would accept the IL-2/LAK data as " supportive evidence." But FDA's Siegel says, "The FDA sees IL-2 and LAK as separate biological agents. The efficacy of IL-2/LAK cannot be extrapolated to IL-2 alone. We told them that." (Wiernik of Albert Einstein believes there is a growing feeling among renal cell carcinoma specialists that it is IL-2, not LAK, that is the therapeutically important ingredient.)

Siegel, who summarized the FDA's position after Cetus finished presenting its case, ended up unable to support the IL-2 application. Challenging much of Cetus's presentation on methodological grounds, Siegel said, "We believe there is a potential bias in the selection of the control group, the selection of methods of statistical analysis done retrospectively, and, most important, selection of the Proleukin IL-2 studies for the analysis." It was hardly a ringing endorsement and stands in contrast to the summaries FDA officials offered in the cases in which the advisory committee recommended drug approval.

Some researchers believe that this episode has cast a shadow over the medical value of IL-2. Says Wiernik, "I attended a lecture recently on the interleukins. When the speaker was finished, the first question was 'How can you say IL-2 works when the FDA just denied an application to sell it?' The FDA advisory committee says it's too toxic. But they forget that the greatest toxicity of all is cancer death."

Wiernik's point speaks to another issue facing the FDA. When a toxic drug is nonetheless the best there is, should FDA allow patients themselves to decide whether to take a risk? AIDS patients have demanded and won changes in the rules for last-ditch therapy for themselves; other victims of terminal disease are beginning to follow.

So, is the Cetus case representative of how FDA will treat biological response modifiers, or is it an aberration? Analysts with whom *Science* spoke seem split. According to one, the view at a recent meeting of chief executive officers seemed to be "so what. It is Cetus's problem," created in part by belief that the company's decision to market IL-2 now was driven by the financial rather than the scientific side of the company. Bruce Mackler, who analyzes the industry for the Association of Biotechnology Companies, puts it this way: "The lesson to be learned by the industry is that preparation, organization of data, and timing are as important as the data themselves."

Indeed, a lot of Cetus's trouble is tied to Wall Street's expectation that IL-2 would sail through the FDA. Absent those expectations, an FDA decision to postpone approval would not be enough to send tremors through the stock market or threaten a veteran biotechnology company like Cetus.

FDA officials say they expect to meet again on IL-2 whenever the company wishes, though no one is predicting when a reconstituted application will be ready.

■ **BARBARA J. CULLITON**