

Expanded Access Programs Vital, but New Rules Raise Concerns

By Donna Young

Washington Editor

WASHINGTON - New FDA rules aimed at clarifying procedures and standards for expanded access to experimental treatments for seriously ill patients could result in higher costs and greater risks for drugmakers, driving down the incentives for companies to take part in such programs, said Emil Kakkis, president of the Kakkis EveryLife Foundation and a former chief medical officer for BioMarin Corp.

But at a debate about the new regulations, which were announced last month and take effect on Oct. 13, others argued the rules were long overdue and would assist in making investigational drugs more widely available to patients. (See *BioWorld Today*, Aug. 13, 2009.)

While the FDA has had regulations in place since 1987 for allowing the use of investigational drugs to treat non-study participants with serious illnesses, regulators have allowed the use of such unapproved drugs in certain situations since the 1970s, noted Rachel Behrman, associate commissioner for clinical programs at the FDA and director of the agency's Critical Path Initiative.

Access to medications for treatment, she said, "is very important to FDA. This is something that we have a long and proud history of doing quite well and caring about."

Behrman noted that some of the first investigational drugs allowed under informal access programs were antiarrhythmics.

In fact, she said, it has not been well known that the approval of the antiarrhythmic amiodarone "was based almost exclusively on expanded access data."

The FDA in 1986 - a year before the first expanded access regulations were issued - approved the first so-called treatment investigational new drug application (IND) for the AIDS therapy azidothymidine, or AZT, Behrman said.

The FDA allows expanded access to investigational drugs in three groups: individual patients, small to intermediate populations and treatment INDs, which are larger populations.

Behrman noted that one drug the FDA has approved for experimental use in an intermediate population is ribavirin to treat hantavirus outbreaks, where there are no drugs to treat the disease, but that drug has shown to be effective.

For treatment INDs, she said, the drug must be one that is actively being investigated in clinical trials designed to support marketing or the studies are completed and the company is actively pursuing approval. There also must be sufficient evidence of safety

and effectiveness, either Phase III or "compelling" data from a Phase II trial, Behrman said.

Gerard Kennealey, vice president of business development at Cephalon Inc., noted that the treatment IND expanded access program for AstraZeneca plc's Iressa (getfitinib) in non-small-cell lung cancer (NSCLC) included 22,000 patients.

Kennealey, a former vice president of oncology clinical research at AstraZeneca, who oversaw the Iressa expanded access program, noted that after results of an early clinical study of the drug, presented in 2000, showed a "dramatic effect" in patients with NSCLC, "we received literally thousands of phone calls" asking for access to Iressa, which has since gained approval as a treatment of patients with locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemotherapies.

Kennealey said an important feature of the program was the determination that "there would be firm rules about entry, with no exceptions made on the basis of persistence or political position," which he said AstraZeneca adhered to throughout the program.

He noted that patients were excluded who were eligible for clinical trials that would support FDA approval "to prevent interference in the process of getting the drug to market."

In his 40-year medical career, Kennealey said, his involvement with the expanded access program was "the most important thing I've done."

Jack Talley, CEO of EpiCept Corp., noted, however, that expanded access programs can be expensive endeavors, especially for small biotechs with "modest" balance sheets.

"The expense of providing access to these drugs is significant for a company, such as ourselves," he said.

The company currently is running an expanded access program outside of the U.S. for its acute myeloid leukemia (AML) drug Ceplene (histamine dihydrochloride), which is approved in the EU for AML, an orphan disease. The company plans to submit an application to the FDA in early 2010, Talley said.

Since its inception, EpiCept has cumulative losses in excess of \$300 million, "and that's all essentially to develop drugs," he said.

The company decided not to pursue an expanded access program in the U.S. partly due to the pricing restrictions, Talley said.

"Outside the U.S. we can choose to price it at a level that we think is responsible enough that allows access to patients and also one that obviously is in excess of the cost of the material," he said.

The other reason the firm has not initiated an access program in the U.S. is because AML is a "very deadly disease," with about 40 out of every 100 patients not surviving more than nine months after diagnosis.

Therefore, Talley said, the firm had to balance that knowledge with the fact that it planned to soon submit its NDA to the FDA, which he said "would have to be evaluating the totality of our data package."

While clinical trials are a "controlled" environment, Talley contended that expanded use programs are an "uncontrolled experience." Nonetheless, he said, "We are very happy with our experience with the expanded access program outside of the U.S."

But Behrman insisted that no drug has ever failed to gain approval based on data from the expanded access program.

"There's not a single product that has ever had its approval jeopardized by an expanded access program," she charged.

But for most companies, Kakkis said, expanded access is "a very difficult challenge and a risk."

"Unfortunately, the new regulations don't really change that," he asserted. "They are mostly logistical and procedural, and those are helpful, but they don't really change the overall risk profile for the companies."

Nonetheless, he said, "Companies have a moral responsibility to be working on these programs and do them."

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