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Debate Continues Over Patient Access to Investigational Drugs

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November 3, 2009 — Patients with cancer and other serious illnesses often seek access to investigational drugs when all other treatment options have been exhausted. The US Food and Drug Administration (FDA) recently published updates to their expanded-access rules in an effort to clarify existing regulations and add new types of access but, as [previously reported](#) by *Medscape Oncology*, the debate over patient access to investigational drugs is expected to continue.

To explore the many issues that still need to be addressed, a panel that included representatives from the FDA, the pharmaceutical/biotechnology industry, patient advocacy groups, and the medical profession, and a bioethicist, was convened by the Idis Foundation and the National Organization for Rare Disorders (NORD). Idis partners globally with the pharmaceutical/biotechnology industry and physicians to help patients acquire drugs through expanded-access programs.

Divergent viewpoints on the topic of access to investigational drugs have evolved.

The specific details of regulations vary around the world, but they all try to provide a mechanism by which patients with unmet medical needs can access drugs that are in development in a safe and regulated manner, explained Natalie Douglas, CEO of Idis. "The questions are: Do these mechanisms work? Do they achieve their aims? Do they enable pharmaceutical companies to make investigational drugs accessible for patients with unmet medical needs?"

"Divergent viewpoints on the topic of access to investigational drugs have evolved and I believe they will continue to evolve," she added.

New FDA Regulations

Panelist Rachel Behrman, MD, MPH, associate commissioner for clinical programs and director of Critical Path Initiative at the FDA, explained that one reason for the recent revision was the need to modernize the regulations to ensure that they reflected the actual options available to patients. Several crucial regulatory points also needed clarification.

"The first point that we're talking about is access for the purposes of treatment," said Dr. Behrman. "We've never acknowledged that in the regulations and it's a very important distinction. We don't have to pretend that we need to fit this into the study paradigm."

She explained that the evidentiary basis by which agents are approved or released varies. For a single patient, the evidentiary basis will be much lower than that for a large-scale access program in which thousands of patients will be exposed.

The charging regulation also had to be updated, said Dr. Behrman. The old charging regulations were confusing, and it was unclear when a company or manufacturer could charge and for what.

"We made it very, very clear," she said. "Access to treatment is not part of the usual cost of doing business and if a company chooses cost recovery, that is an option absolutely open to them."

We will be removing obstacles.

The FDA does not want to be an obstacle, she explained, and "we will be removing obstacles."

Under the new regulations, a company can recover the cost of the product, but it cannot make a profit.

Iressa Expanded-Access Program

As an example of a successful expanded-access program, medical oncologist Gerard T. Kenealley, MD, vice president of business development at Cephalon, recounted his experience with gefitinib (*Iressa*).

Gefitinib inhibits the catalytic activity of numerous tyrosine kinases, including the epidermal growth-factor receptor. When it was first discovered, it was part of a new class of drugs, explained Dr. Kenealley. Dramatic results were seen in about 10% of the patients with nonsmall-cell lung cancer.

"These results were such that many people in the media called Iressa a 'Lazarus' drug," he said during the panel discussion. "It clearly didn't help everybody, but it did help dramatically a very small number of patients with nonsmall-cell lung cancer."

Study results were first presented to the medical community in May 2000, and "caused quite a splash in the media," said Dr. Kenealley. As a result, AstraZeneca, the manufacturer of gefitinib, received literally thousands of phone calls asking for access to the agent.

The company had no prior experience with expanded access and turned to the FDA for assistance, explained Dr. Kenealley, who was working for AstraZeneca at the time. "They were instrumental in helping us design an expanded-access program for Iressa," he said.

The first step was to make a commitment to the process and to dedicate the necessary resources to make it succeed. A team was created and the help of organizations such as NORD, the FDA, and advocacy groups was enlisted. "A single informed consent form was carefully developed and an important feature was the determination that there would be firm rules about entry into the program," he said.

Because the best way to get a drug to a patient is to get it on the market, Dr. Kenealley explained that "we had to be sure that we limited the expanded-access program to patients who were not eligible for the trials."

Despite imposing narrow limitations of eligibility, 22,000 patients eventually became part of the expanded-access program. If the 10% response rate seen in clinical trials carried over to the population in the expanded-access program, then 2000 patients were helped, he said.

Burden to Companies, Lack of Incentives

Despite changes in regulations, many drug manufacturers are still reluctant to offer access to their investigational products. "I think, for most companies, it's looked at as a very difficult challenge and a risk only, and that there is little chance for improvement or benefit to them," said Emil Kakkis, MD, PhD, president of the Kakkis EveryLife Foundation, an advocacy group for patients with rare diseases. "It becomes a serious burden and, unfortunately, the new regulations don't really change that."

I don't think it's going to change the rate of access to investigational drugs.

Dr. Kakkis believes that the changes in regulations are primarily logistical and procedural, and although helpful, are not going to change the overall risk profile for companies. "From my own experience, I don't think it's going to change the rate of access to investigational drugs, and I think that the disincentives and risks for companies right now make it very difficult for them to want to do expanded-access programs," he said.

"For companies, and I think for many in the FDA, the goal is simply to get the drugs developed and approved, and they do not want to be distracted by this," he added.

That is a mistake, contends Dr. Kakkis, who thinks that companies have a moral responsibility to be working on these programs. He notes that not only do the new regulations leave incentives and risks unchanged, they might, in fact, be making them worse. "I think that they're actually going to reduce the desire for companies to do expanded access," he said.

As an example, he pointed out that the FDA is going to require full safety reporting for patients in compassionate-use programs, which goes beyond just the documentation of expected adverse events.

"I think the natural fallout from that will be the need for more staff to follow up and to ensure that all adverse events are being captured, not just serious ones," Dr. Kakkis said. "I think that's a change that seems sensible but, in fact, will change the risk profile for companies doing this work. I think for many companies, it probably will reduce their desire to take on compassion-use challenges."

Expanded Access Beyond American Borders

Panelist Jack Talley, president and CEO of EpiCept, explained why his company decided to offer *Ceplene* (histamine dihydrochloride), their drug for acute myeloid leukemia (AML), to expanded-access programs outside the United States. EpiCept is a small biotechnology company that is focused primarily on the development of oncologic drugs and agents for the treatment of pain.

Ceplene is an approved and an investigational drug, said Mr. Talley. It has been approved in the European Union for the treatment of AML, whereas elsewhere in the world it is an investigational drug. The company has filed for approval in Canada and is preparing a New Drug Application to be filed with the FDA in early 2010. "If we do get priority review, as expected, we would be facing an approval decision by the FDA in the latter part of 2010," said Mr. Talley.

Mr. Talley describes EpiCept as a "relatively modest company, what we call thinly capitalized."

Programs to develop new drugs are extraordinarily expensive, according to Mr. Talley. Since its inception, EpiCept has experienced cumulative losses in excess of \$300 million. "That's all essentially to develop drugs. We did not pretend that we were going to come anywhere near that figure with the expanded-access program," he said "Our only ability to ever recoup those costs is going to be through the eventual commercial marketing of the products that we develop."

Pricing restrictions is one of the primary reasons for EpiCept's decision not to offer an expanded-access program in the United States. "Outside the United States, we can choose to price [Ceplene] at the level that we think is responsible enough to allow access to patients, and also one that obviously, in our case, is in excess of the cost of production of the material," he said.

"We feel it would be easier to implement this type of program in the United States if we had an even more relaxed ability to price our product without restrictions," he added.

Converging Themes

From a bioethics point of view, there is a need to protect human subjects in biomedical research, but tension exists "between "individual medical judgment, for the benefit of an individual patient, and the goal of scientific research to produce generalizable knowledge from populations," explained panelist Lee L. Zwanziger, PhD, adjunct professor of bioethics at Virginia Polytechnic Institute and State University in Blacksburg.

"The themes that we see — and have been seeing in the tensions surrounding access to investigational products — I think are similar or related," she said. "These include autonomy and respect for persons, balance of benefit and risk for the individual participants, and justice in the distribution of benefits and risks for the larger society."

"I think we have some common ultimate goals of access to effective and safe therapies as soon as possible for all those who need those products," she explained. "But intermediately, we have different perspectives that lead to different and even conflicting courses of action."

Dr. Zwanziger added that "individuals and organizations choose to advocate for different perspectives, and I think these multiple perspectives kind of help us keep some balance."

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