IN brief

FDA penalizes trial misconduct

Synthetic Genomics

Hamburg takes a tough stance

The US Food and Drug Administration (FDA) has gotten tough with investigators who flout the rules during the course of clinical studies. Researchers face debarment and disqualification if patient safety and public health is threatened under the agency's newly enhanced procedures announced on August 7, 2009. The initiative is intended to address perceptions that the agency has been performing poorly. Newly appointed FDA Commissioner Peggy Hamburg admitted in a speech that the agency has a reputation for "back and forth, stall and delay, let's see what the company does," promising to take strong action. Efforts to expedite the disqualification and debarment processes began much earlier, in June 2007, when regulators noticed that penalties for misconduct were taking a long time to process. During this time the FDA implemented a series of changes but Joanne Less, director of the Office of Good Clinical Practice at FDA explains, "We had a backlog of pending disqualification matters in 2007, so in the beginning of 2008 we focused on clearing out that backlog."

Disqualification is applied to a trial investigator who violates FDA regulations during the course of a clinical study. Debarment permanently bans individuals or companies from the drug industry who have been convicted of felonies or misdemeanors related to drug development. Notable violations include failure to obtain informed consent, falsification of data, fabrication of patient enrollees, lack of control or documentation of drug supply, and various administrative violations. Investigators targeted for disqualification or debarment receive a notice from the FDA and an opportunity to either correct the infraction or dispute the findings, depending on the situation.

Lists of disqualified and debarred entities will be available on the FDA website (http://www.fda.gov/)—an important resource for companies who are responsible for making sure their investigators are qualified to carry out studies. The agency's tougher standards also reward companies with good compliance practices. In general the new process is good for the industry and good for the public, but some of the regulations are complex, and ensuring compliance is challenging. Kim Egan, a partner in law firm DLA Piper's Life Sciences practice in Washington, DC, offers regulatory advice to pharma. "We're seeing a little uptick in FDA inspections. We help our clients maneuver through the issues there," she says. "Small biotechs and startups have a challenge because they don't have a lot of resources."

Catherine Shaffer

of infectious diseases and medicine development at GlaxoSmithKline's Research Triangle Park campus in North Carolina, recalls his experience with influenza treatment Relenza (zanamavir) when it was still in phase 3, and physicians called to request the drug for very sick patients. "There was some resistance [to provide the drug] because when you're treating patients who are very ill and with end-stage congestive heart failure or who are immunocompromised, and the patient dies, your label will have all this bad stuff on it," he says. "They wanted to save these lives, but they also wanted to get the drug approved."

Expanded access can pose financial difficulties too. For instance, President and CEO Spiro Rombotis of Berkeley Heights, New Jersey–based Cyclacel Pharmaceuticals would like to set up a treatment protocol for expanded access to his company's nucleoside analog sapacitabine (CYC682) currently in phase 2 for acute myeloid leukemia (AML) and myelodysplastic syndromes. The 20-odd hematology and oncology investigators who have been participating in the studies have been asking for a program to rescue patients in need. But in the current economic climate it is difficult for small development-stage biopharmas to raise capital, and whatever funds are available need to be directed to pivotal trials that might support approval. Nevertheless, Rombotis points to an 82-year-old man with AML who was given little chance of surviving beyond a few weeks in 2007, when he received expanded access to sapacitabine, then only in phase 1. "He achieved two more birthdays," he says. "We would like to be able to do more of this."

The new rules stipulate that companies can charge for experimental drugs, but that the price must reflect the actual costs, which includes the product itself and associated overheads. "This is not a trivial change," says Cyclacel's Rombotis. "It's a little naive to expect a manufacturer to tell what it really costs." The problem for drug manufacturers is that they consider their costs to be trade secrets, and as such do not want to reveal them to competitors, payers or to potential partners. Indeed, some companies would rather provide the product at no charge if possible, which is easier said than done for small biotechs that are already burdened by lack of access to capital. "In theory, small companies can charge for drugs supplied under expanded access programs, but it requires FDA approval, and it may not yield enough income to offset the extra administrative costs," says industry lawyer Kingham.

The patient advocate camp is not pleased either, even though the FDA estimates more than 3,000 additional individuals per year will receive access to experimental drugs thanks to the changes. Abigail Alliance CEO Frank Burroughs says, "The agency has missed an opportunity with these new rules." He points out that tens of thousands of people want access to experimental drugs, and a much broader expanded access would be possible without disrupting the drug approval process. "It falls way short," he says.

The Alliance wants to provide incentives to companies to allow expanded access, limit the FDA's ability to block such access and protect companies from noncriminal liability claims associated with expanded access. These points are all part of the Alliance's Access Act, which the Alliance will be discussing this December at a meeting with new FDA commissioner Margaret Hamburg and principal deputy commissioner Joshua Sharfstein. "We're focused on that meeting," Burroughs adds. Given the 'change mandate' that Hamburg and Sharfstein are thought to represent, pharmaceutical and biotech companies will likely be watching as well.

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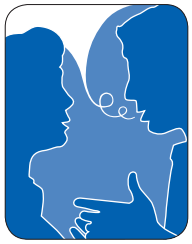
IN their words



"What will happen one day when someone tests something and finds out that organics is contaminated beyond a reasonable amount, say 5 or 10%? Consumers would lose all faith in organics." Dag Flack, board member of Nature's Path, explaining the rationale for a new campaign from the Non-GMO Project to test and label products free of GM ingredients. (*New York Times*, August 28, 2009)

"There should not be any industry funding of a group that is involved in working on national guidelines." Jerome E. Groopman, professor of medicine at Harvard, pronounces on the raging controversy over guidelines for aggressive blood glucose control after a study suggested that such action could harm or even kill some patients. (*New York Times*, August 18, 2009)

"It's the most amazing polarity that I've seen. It's like two religions fighting." Michael E. Clarke, the Stanford researcher who discovered cancer stem cells in breast tumors, on how controversy over the importance of these cells has split researchers in the field. (*New York Times*, August 13, 2009)