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## BUSINESS AND REGULATORY NEWS

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### Inquiry into gene therapy widens

Julie Grisham

Scrutiny of gene therapy continued in February when a US Senate subcommittee held a hearing to discuss current oversight procedures, in light of revelations that only 6% of serious side effects in certain gene therapy clinical trials had been reported to the US National Institutes of Health (NIH; Bethesda, MD). Industry has proposed a plan to bolster its reporting of safety data to NIH, which has outlined its own efforts to remedy the situation.

In late January, the US Food and Drug Administration (FDA; Rockville, MD) put on hold all human gene therapy trials at the Institute for Human Gene Therapy at the University of Pennsylvania (UPenn; Philadelphia, PA), where 18-year-old Jesse Gelsinger died while participating in a phase I clinical trial last September for an inherited liver disorder called ornithine transcarbamylase deficiency (*Nat. Biotechnol.*, **18**, 143–144). FDA said a nearly two-month-long inspection at UPenn had turned up "numerous serious deficiencies in the procedures in place for oversight and monitoring of the clinical trials" for gene therapy. It said that because of those concerns, it believed subjects in the UPenn trials could be "exposed to a significant and unreasonable risk." Among the corrections it noted the university must make before trials could resume were conducting studies in accordance with clinical protocols, obtaining proper informed consent from subjects, filing safety reports, and maintaining complete and accurate records.

In investigations that followed Gelsinger's death, it also became clear to officials at NIH that the number of serious adverse events occurring in gene therapy clinical trials (such as high fevers, infections, severe changes in blood pressure, or even deaths) had been vastly underreported. In fact, 652 serious adverse events related to use of the adenovirus in gene therapy over a seven-year period had gone unreported to the Recombinant DNA Advisory Committee (RAC), a public body that advises NIH on gene therapy clinical protocols. That is, they were unreported until the agency sent out a call to gene therapy investigators requesting more information on adenovirus safety and toxicity. Previously, RAC had received reports on only 39 such events.

Under NIH funding guidelines, researchers who receive money from NIH or work at institutions that do must report these events to the agency. In a letter to Rep. Henry A. Waxman (D-CA), who had requested more information from NIH on gene therapy, NIH Acting Director Ruth L. Kirschstein wrote she was "deeply concerned about the under-reporting of serious adverse events to the NIH" and that her agency was taking steps to address the problem "expeditiously." She said although the letters explaining the guidelines to investigators are "explicit, ... they clearly have not accomplished what we intended."

Many experts attribute the lack of reporting to confusion over what the requirements were. Savio Woo, director of the Institute for Gene Therapy and Molecular Medicine at Mount Sinai School of Medicine (New York) and president of the American Society of Gene Therapy, says, in his opinion, investigators wrongly made the assumption that because RAC deals with DNA, they only had to report DNA-related events. Unlike Gelsinger, whose disease was under control with diet and medication, many patients who participate in gene therapy trials are already very sick, and the majority of adverse events have been attributed to the underlying diseases for which the patients were being treated, not to the therapy.

On Feb. 2, a subcommittee of the US Senate Committee on Health, Education, Labor, and Pensions held a hearing to discuss whether current oversight of gene therapy trials is sufficient. In his opening statement, the Public Health Subcommittee chairman, Sen. Bill Frist (R-TN), expressed great concern over the unreported deaths and adverse events in gene therapy trials.

In his testimony, Jay P. Siegel, director of the Office of Therapeutics Research and Review at FDA's Center for Biologics Evaluation and Research, explained FDA's reporting requirements, which are different from those of NIH. Under the rules for all investigational new drug applications, which include gene therapy, both sponsors and investigators have regulatory responsibility to report serious and unexpected events to FDA, and that agency has not expressed any concerns about under-reporting. However, unlike the reports to RAC, the information given to FDA is not made public.

Amy Patterson, director of the Office of Biotechnology Activities at NIH, admitted at the hearing that there had been major problems in that reports were being made only to FDA, but said her agency was taking immediate steps to ensure such mistakes do not occur in the future. These steps include establishing a new process for information sharing between NIH and FDA, taking steps to prevent trial sponsors such as biotech companies from holding information back by labeling it proprietary, and setting up a working group to assess the current reporting requirements.

Sen. Frist suggested at the hearing that there may be need for additional legislation to ensure proper oversight of gene therapy trials. However, Stewart Parker, CEO of gene therapy company Targeted Genetics (Seattle, WA), says it is important that everyone involved in gene therapy works together to maximize compliance to current rules before additional regulation is considered.

Testifying on behalf of the Biotechnology Industry Organization (BIO; Washington, DC), Parker said that BIO members welcome and expect strict oversight from FDA, and support a plan in which RAC would receive the same serious adverse event reports that FDA does. Under the BIO plan, RAC would receive not only reports already required from investigators under NIH funding guidelines, but also would get company reports on safety related to gene therapy—something currently required by FDA only. She says NIH would be responsible for ensuring patient privacy confidentiality and maintaining proprietary information when the information was made public.

Woo also is strong advocate of FDA and NIH/RAC having harmonized reporting requirements. He says it's important that the two agencies "put their heads together" because different requirements create confusion and are a "breeding ground for noncompliance."

The revelations about the problems with human gene therapy at UPenn have had effects on other trials. Already, a gene therapy trial at Beth Israel Deaconess Medical Center (Boston, MA) has been suspended because of concerns about the safety of such procedures. And the Muscular Dystrophy Association (MDA; Tucson, AZ) and the Cystic Fibrosis Foundation (CFF; Bethesda, MD) both have put a halt to some gene therapy trials they were sponsoring. MDA suspended funding for its gene therapy trial being conducted under the aegis of UPenn's Institute for Human Gene Therapy, and CFF has suspended all trials using the adenovirus vector.

Nevertheless, both Parker and Woo say they believe the public still has faith in the promise of gene therapy and wants it to continue. Woo points out that no new therapies can go forward without clinical trials, and therefore those trials must go on. But he says it's important for investigators to learn to do things better—to develop better vectors for introduction of genetic material, create better informed consent rules, and do a better job reporting adverse events.

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