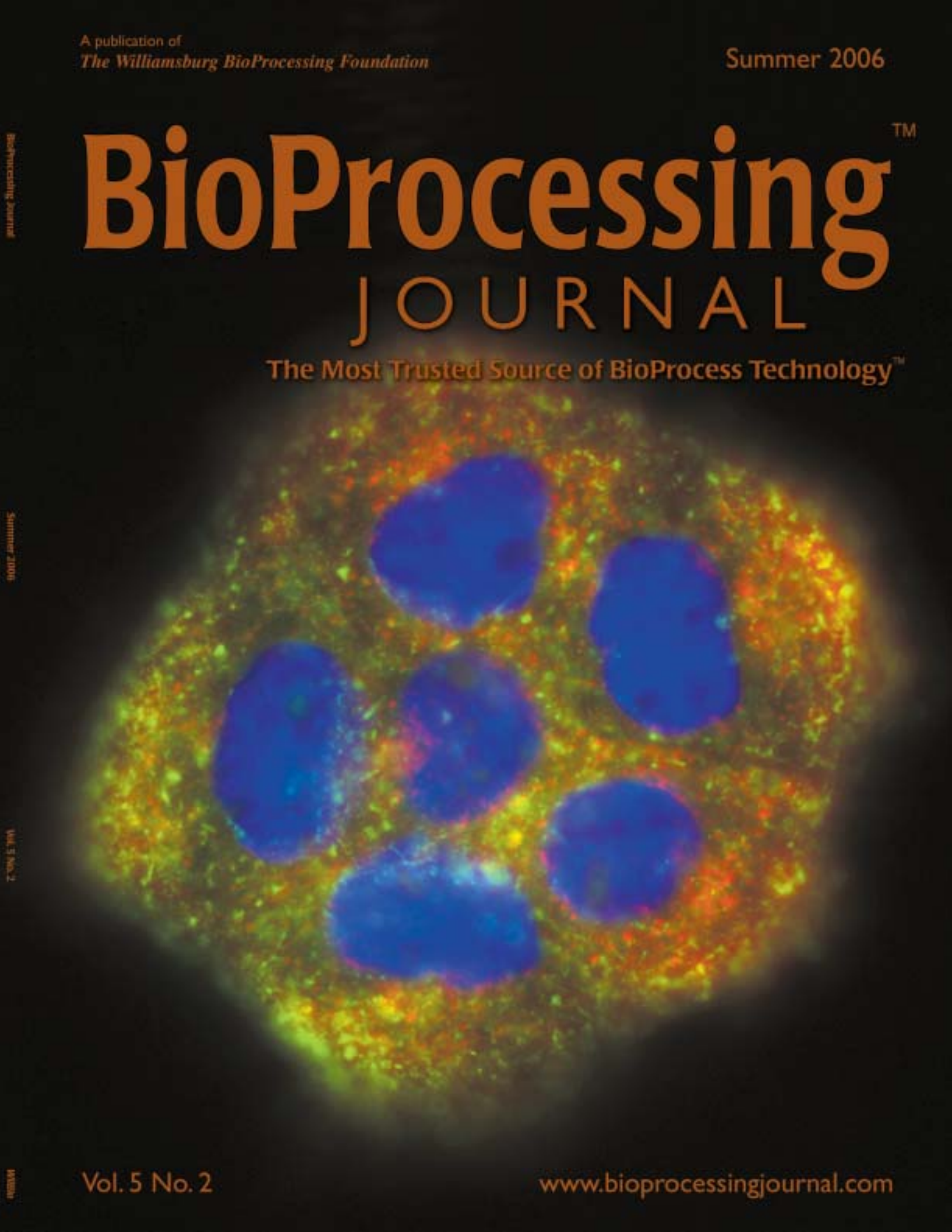
A publication of
The Williamsburg BioProcessing Foundation

Summer 2006

BioProcessing™ JOURNAL

The Most Trusted Source of BioProcess Technology™



Vol. 5 No. 2

www.bioprocessingjournal.com

Regulatory Overview of Conducting Gene Therapy Clinical Trials in the United States

By WILLIAM LEE

Since the first gene therapy trials were conducted 25 years ago, there have been high expectations from the public, and much attention from investors, that previously incurable diseases would be cured by gene therapy. Still, despite numerous gene therapy clinical trials for many different indications, there are no approved gene therapy drugs in the United States.

In 1999, one gene therapy patient died during clinical trials, the first ever. This highly publicized event led to heightened regulatory scrutiny over all such trials. Then in 2003 and 2005, three subjects developed leukemia as a direct consequence of gene therapy; one of them eventually passed away. The regulatory response stemming from these incidents led to greater regulatory oversight in gene therapy, as compared to other investigational drugs and biologics. These significant events are outlined in Table 1.

Table 1. A history of gene therapy clinical trials.

1980	First gene therapy trial by W. French Anderson for the treatment of adenosine deaminase therapy.
1999	Death of Jesse Gelsinger, 18-year-old participant in an ornithine transcarbamylase deficiency (OT3) trial, of a massive immune response to the vector. Leading to increased oversight by NIH, harmonized requirements for expedited adverse event monitoring between FDA and OBA/NIH, and the eventual formation of a working group to establish adenoviral vector reference standard.
1999	Finding of introduced HIV/hepatitis C (HCV) sequences in the adenoviral vector in a trial at St. Jude's Hospital. Leading to requirement for sequencing up to 40 kilobases of all gene therapy vectors.
2000	FDA sent letter to gene therapy IND sponsors or master file sponsors requesting information on clinical monitoring and manufacturing of gene therapy products.
2003	Development of leukemia in three "bubble boys" (including one eventual death) who had been cured three years earlier of the fatal immune disease SCID-X1 with *ex vivo* gene transfer using a retroviral vector and CD34+ progenitor cells. Leading to requirement for monitoring of subjects for 15 years after completion of all clinical trials involving vectors that integrate into host cell DNA.
2003	FDA suspension of 27 trials using retroviral vectors and hematopoietic stem cells, with case-by-case resumption after review, and an increased requirement for informed consent and long-term monitoring of patients.

This short review touches on the recent history of gene therapy and its resulting impact on the state of our current regulatory environment. It concludes with the current regulatory requirements of a sponsor for initiating, conducting, and following up with a gene therapy clinical trial in the U.S. Table 2 displays the overall structure of regulatory oversight in the U.S. for gene therapy. The first column shows the regulatory oversight that applies to clinical trials of all investigational drugs or biologics. The second column displays the regulatory oversight that applies only to clinical trials of gene therapy products in the U.S. As will be discussed later, there is oversight at both the federal and local levels, and different scopes of regulatory review.

Regulatory Oversight By Federal Agencies

There are two federal agencies that regulate gene therapy clinical trials in the United States, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH). For all investigational agents to be tested in clinical

William Lee, Ph.D., *(wlee@cato.com) is a regulatory scientist with Cato Research, Durham, North Carolina.* *This article is based on a presentation given at the Williamsburg BioProcessing Foundation's Second Annual WilBio–Asia: Viral Vectors and Vaccines conference held September 5-7, 2005, in Singapore.*

trials, there is the regulatory oversight by the FDA. For those that incorporate gene therapy, regulatory oversight is administered by an additional agency, the Office of Biotechnology Activities (OBA) within the NIH. The FDA and OBA can be viewed as two parallel tracks of regulatory review for clinical trials in gene therapy.

The nature of review between these two agencies can be regarded as somewhat complementary in scope. Both agencies strive to protect the welfare of the participants in gene therapy clinical trials. Because of its mission to protect participants from undue risk, the FDA concentrates on ensuring that sponsors create safe, high quality gene therapy products. To that end, FDA focuses on the manufacturing aspects of the product while relying heavily on non-clinical toxicology studies. The purview of the NIH has been to evaluate the quality of the science itself, focusing on the technical aspects of vector design, non-clinical proof-of-concept studies, and vector immunology.

Table 2. Regulatory oversight of gene therapy clinical trials in the United States.

Federal Authority	FDA – Office of Cellular, Tissue and Gene Therapy	NIH – Office of Biotechnology Activities
Local Authority	IRB	IBC
Adverse Event Reporting	MedWatch form	MedWatch form or OBA/NIH Reporting Template
Nature of Regulatory Review	◆ Confidential ◆ Safety and Product review by FDA reviewers	◆ Public ◆ Critical scientific review by leading academic researchers

Food and Drug Administration

Clinical studies involving gene therapy are regulated by FDA's Office of Cellular, Tissue and Gene Therapies within the Center for Biologics Evaluations and Research (CBER). This office reviews gene therapies involving genetic diseases such as cystic fibrosis, cancers, and cardiovascular disease. These clinical studies include, for example, the adenovirus-associated vector encoding the cystic fibrosis transmembrane conductance regulator (CFTR) gene as a treatment for cystic fibrosis, or adenovirus vector encoding p53 as a treatment for head and neck cancer. However, if the clinical study involves gene transfer and is intended to be used as a vaccine against infectious diseases, then the study is regulated by the Office of Vaccines Research and Review (OVRR) within CBER. These clinical studies include, for example, the adenoviral vectors encoding HIV *gag* antigen as a vaccine against HIV.

Office of Biotechnology Activities/ National Institutes of Health

In the 1970s, the first genes were cloned. Public hostility and concern about genetic engineering led the NIH to establish the Recombinant DNA Advisory Committee (RAC) to review all research on recombinant DNA (rDNA) research, including oversight of human gene therapy experiments. The RAC has since been placed within the OBA.

The RAC reviews all gene therapy clinical trials in every institution receiving NIH funding for rDNA research. This covers the following: 1) clinical investigators participating in clinical trials who receive NIH funding; 2) clinical investigators who are affiliated with institutions that receive NIH funding; or 3) clinical trials conducted at institutions that receive NIH funding.

The unique aspect of the RAC review protocol is that technological advances in gene therapy clinical trials are brought forth into a public discussion forum that meets quarterly. To merit this type of discussion, the criteria to be judged are: 1) novelty of the vector; 2) gene delivery system; 3) disease; and 4) application of gene transfer. For example, public discussion issues included clinical trials that have utilized the first HIV vector, application of RNA interference (RNAi), and adenoassociated viral (AAV) vector. The RAC brings to bear critical scientific review by the leading academic researchers.

Clinical protocols deemed not to be novel or of significant risk undergo an accelerated review process consisting of written reviews of the clinical protocol and informed consent by members of the RAC committee outside of the quarterly public meetings.

Regulatory Oversight By Local Authorities

At the local level, oversight of gene therapy clinical trials are conducted by two separate bodies composed of scientists and individuals from the community, the Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC). The IRB approves the clinical trial within the institution serving as the trial site while the IBC operates under the auspices of the NIH and is analogous to the IRB. The IBC reviews and approves all gene transfer experiments in human research participants to be conducted at the proposed clinical trial site.

The Gelsinger Gene Therapy Trial Incident and its Effects On Regulatory Oversight

The death of 18-year-old subject Jesse Gelsinger brought many changes to the regulation of gene therapy, most notably, reforming structural oversight by RAC and IBC, and harmonizing the FDA and NIH reporting requirements for adverse events.

FDA Response

Following the Gelsinger incident, the FDA initiated a survey of current gene therapy clinical trials by sending a letter to all holders of gene therapy investigational new drug applications (INDs) and master files, asking for detailed information regarding monitoring of clinical trials and manufacturing of the

gene therapy product. In addition, the FDA conducted random inspections of 70 clinical trials. The FDA realized that a large portion of the investigators needed to be educated on good clinical practice and the proper procedures for clinical monitoring. This led to educational outreach programs such as those conducted as a pre-meeting before the American Society of Gene Therapy (ASGT) annual meetings, and a series of gene transfer safety symposiums, training programs on IND preparation, and clinical monitoring.[1]

The FDA also launched a database called the Gene Therapy Patient Tracking System (GTPTS), devoted exclusively to gene therapy. This database allows tracking of patients that initially undergo gene therapy treatment and then transition into another follow-on study requiring long-term follow-up. This database also allows a comprehensive examination of patients that have undergone gene therapy across multiple INDs within a vector class.[2]

RAC Response

The Gelsinger incident led to a re-examination of the oversight system by the RAC and IBC. Previously, the RAC committee had no authority to place a gene therapy clinical trial on hold. Their purpose was to evaluate the clinical protocol and offer advice on how to proceed—only the local IBC could delay or prevent the trial from proceeding. Since these two agencies were not required to communicate with each other, the IBC wasn't necessarily aware of the RAC committee recommendations. Occasionally, the IBC allowed the trial to proceed before the public RAC debate had taken place.

After Gelsinger's death, the NIH guidelines for research involving recombinant DNA molecules (NIH Guidelines) were amended. One major amendment was made in 2000, wherein clinical protocol recommendations from the RAC committee are forwarded to the investigator, FDA, IRB and the IBC, and the IBC will wait for the advice of the RAC before granting permission to initiate a trial. The IBC must consider issues raised and recommendations made during RAC review before allowing a trial to proceed. This mechanism effectively grants the RAC committee the power to delay the initiation of a clinical trial.[3]

Before the Gelsinger incident, the requirements for expedited reporting of serious adverse event reporting during gene therapy clinical trials were different between FDA and RAC/NIH. The FDA required expeditious reporting of serious adverse events that were related and unexpected, whereas the NIH required reporting of all serious adverse events. In addition, the accelerated submission timeframes for reporting these events differed between FDA and RAC/NIH. This resulted in confusion and noncompliance among clinical investigators—only 37 of 970 adverse events were reported to the NIH.[4]

Now that these regulatory oversight regulations have been implemented, synchronization exists between FDA and OBA regarding the expeditious reporting of serious adverse events. Now, the same report form, the same timeframe of reporting these events, and the same types of adverse events are submitted to the FDA, OBA, IRB and IBC.

Public Access to Information Regarding Gene Therapy Clinical Trials

In addition to the regulatory reforms put in place subsequent to the Gelsinger incident, a new website, Genetic Modification Clinical Research Information System (GeMCRIS) was launched as a service to the public. Hosted by the OBA and FDA, GeMCRIS now helps provide insight into gene therapy trials and allays safety concerns about them. From this website, the public can gain access to scientific and non-scientific abstracts of the clinical protocols and enrollment information. They can also look up brief, narrative descriptions of serious adverse clinical trial events, including those considered associated and unexpected, which are posted on a quarterly basis.[5]

Establishment of a Reference Standard for Adenoviral Vectors

Sponsors of clinical trials utilizing adenoviral vectors, prior to the Gelsinger incident, characterized the quantity and quality of them according to their own standards. Thus, the FDA wasn't able to compare the quantity of adenoviral vectors between clinical trials utilizing adenoviral vectors from different sponsors. The Gelsinger death was directly attributable to the quantity of adenoviral vectors administered. The RAC followed up by issuing a report in January 2003 recommending the development of an adenovirus reference testing agent. A consortium of academia, industry, and the FDA, coordinated by the Williamsburg BioProcessing Foundation, set up a working group to establish an adenovirus reference protocol, and standardized procedures for testing and characterizing production lots. Specifically, this would define the particle unit and infectious unit for adenoviral vectors and establish a reference point for comparison, allowing the FDA to compare the quantity of products across different sponsors.[6,7]

In their July 13, 2001 advisory committee minutes, the FDA proposed the following requirements for the sponsors of gene therapy clinical trials utilizing adenoviral vectors: 1) the sponsor's analytical methods should be validated against the reference standard; 2) the patient dose should be based on vector particle units; 3) every lot should have less than 30 viral particles per infectious unit; and 4) every clinical lot should have less than one replication competent adenovirus per 3×10^{10} vector particles.[8,9]

In the fall of 1999, an incident at St. Jude Children's Research Hospital prompted stricter characterization of all gene therapy products. The presence of inadvertent HIV/HCV sequences in the adenoviral vector intermediate was discovered during a gene therapy trial for neuroblastoma. This led to the FDA recommendation that all gene therapy vectors be sequenced in their entirety, or up to 40 kb, before its use in a Phase 1 clinical trials.[10]

Another consortium of academia, industry, and the FDA was assembled, coordinated by the Williamsburg BioProcessing Foundation—this time to establish an AAV reference proto-

col, and standardized procedures for testing and characterizing production lots. This allowed the FDA to compare the quantity of AAV vector products administered to subjects across different sponsoring clinical trials.[11]

The Effects of the SCID-X1 Incident on Regulatory Oversight

In 2000, there was a report that nine out of 11 gene therapy trial subjects appeared to be cured of the fatal x-linked severe combined immunodeficiency disease (SCID-X1) after *ex vivo* gene transfer (with retroviral vector encoding the gamma-c cytokine receptor subunit of interleukin-2, -4, -7, -9, and -15 receptors). Announced after the Gelsinger incident, the results of this study provided a hopeful sign that gene therapy was finally fulfilling its promise. Unfortunately, three years later two subjects developed leukemia, and later a third, as a direct consequence of the gene therapy. This created another setback to the gene therapy community—what was touted as the definitive example of a gene therapy that cured patients was now viewed as harmful instead.

The FDA and RAC quickly addressed the situation as an incident related only to retroviral mediated gene transfer in hematopoietic stem cells, and not to the whole field of gene therapy. The FDA applied the following regulatory actions for gene therapy clinical trials utilizing retroviral vectors in hematopoietic stem cells: 1) appropriate information must be in the informed consent; 2) there will be long-term monitoring of participants; and 3) monitoring peripheral blood cells must be conducted for the clonality of vector integration.

The FDA had suspended 27 gene therapy clinical trials using hematopoietic cells transduced with retroviral vectors. After conducting a case-by-case review, FDA allowed these gene therapy clinical trials to resume. As a direct consequence of the SCID-X1 trial, the FDA now requires that sponsors conduct a 15-year follow-up of all subjects treated with gene therapies involving vectors that integrate into the DNA. [12-15]

An Overview of Current Regulatory Obligations

Before initiating a gene therapy clinical trial conducted in the United States, the proper regulatory documents must be submitted to the FDA, OBA, IRB and IBC organizations.

FDA

Prior to submitting the required regulatory application, it is advisable for sponsors to meet with the FDA to solicit feedback regarding the design of the clinical and non-clinical trials. These meetings are not mandatory, but it is beneficial to allow an introduction of the sponsor and the gene therapy product to the FDA before commencing a formal review.

As compared with other investigational drugs, the FDA grants one additional meeting for the sponsor of gene therapy drugs. This "pre-pre-IND" meeting, typically conducted as a teleconference, is where FDA offers informal advice very early in the development of the gene therapy drug. They focus only on pharmacological and toxicological issues—advice specific to the design of the toxicological studies in nonrodent species. Prior to this meeting, a brief package describing the gene therapy product, clinical trial objectives and subject population, proof-of-concept, and initial toxicity studies should be submitted to the FDA.

The "pre-IND" meeting is a formal one, generally conducted face-to-face, with the focus on FDA providing their input into manufacturing issues and the design of Phase 1 clinical trial. The sponsor's meeting package should contain sufficient information for the FDA to provide advice on the proposed clinical trial—information summarizing the results of pharmacology and toxicology studies, manufacturing specifications, and a detailed synopsis of the first clinical trial.

The sponsor must submit a completed IND application to the FDA before initiating the clinical trial. This IND must contain: 1) a discussion of results of the proof-of-concept in animal models; 2) a scientific rationale for the proposed clinical protocol; 3) full reports from the toxicology test results; and 4) reports characterizing the gene therapy product. The IND application, as detailed in the Code of Federal Regulations 21.CFR.312.23, must contain the following elements: 1) the completed Form FDA 1571; 2) a table of contents; 3) an introductory statement; 4) the general investigational plan; 5) the investigator's brochure; 6) the clinical protocol for the planned study; 7) chemistry, manufacturing, and controls information; 8) pharmacology and toxicology information; and 9) previous human experience with the investigational drug. There should also be an analysis of the immune response against both the vector and the gene product. The FDA also requires studies of vector biodistribution addressing what tissues are transduced, and particularly, whether there is evidence of germ-line transfer after vector administration.

In public meetings, the FDA has stated that a monitoring plan must be submitted in the initial IND. Subjects involved in clinical trials utilizing vectors that integrate into the host cell DNA, such as retroviral vectors, AAV and HIV-based vectors, must be monitored for adverse events for a period of 15 years following the completion of the clinical trial.

For clinical trials utilizing vectors that are first in its class for human use, the FDA or IRB may mandate a Data Safety Monitoring Board during the first clinical study.

RAC/OBA

The principal clinical investigator from the proposed site must submit an application to OBA, prior to or concurrent with the IND submission, containing the following: 1) a letter signed by the principal investigator acknowledging compliance with NIH guidelines for research involving recombinant DNA molecules; 2) a scientific abstract; 3) a non-technical abstract; 4) the proposed clinical protocol; 5) the proposed informed consent document; 6) responses to specific questions in M-II through M-V in the abovementioned NIH guidelines; and 7) *curriculum vitae* of the principal inves-

tigator. If the clinical trial involves public discussion by the RAC, then the submission should be accomplished eight weeks before the next scheduled RAC meeting so it can be scheduled.

IRB

The principal investigator at the site of the proposed clinical trial must submit the following documents to the IRB: 1) the clinical protocol; 2) the investigator's brochure; and 3) the informed consent form.

IBC

An application must be submitted to the IBC by the principal investigator of the proposed clinical trial site. The application must contain the following elements: 1) information on the source of the DNA; 2) the nature of the inserted DNA sequence; 3) gene transfer vectors to be used; 4) information on whether an attempt will be made to obtain expression of a foreign gene, and if so, which protein that will be produced; and 5) containment conditions to be implemented.

Only after 30 days of no comment from the FDA, after the submission of the IND application, and approvals from IBC and IRB, can the principal investigator begin enrolling patients in the clinical trial.

During the Clinical Trial

Regulations governing clinical trial conduct or monitoring of gene therapy clinical trials are no more stringent than for other clinical trials involving other investigational drugs or biologics. However, due to the nature of gene therapy, there are two specific assays required by the FDA: 1) monitoring subjects' immune response to both the vector and the transduced gene product; and 2) monitoring the presence of vector in semen. The Gelsinger tragedy was most likely triggered by a massive immune response to the adenoviral vector; therefore monitoring the immune response to the gene therapy vector is highly recommended for safety. If the gene therapy is not a vaccine, then an immune response to the transduced gene product will negate any therapeutic effect. Monitoring the immune response to the transduced gene product is, for that reason, recommended as an indication for efficacy. Secondly, inadvertent gene transfer into the germ line is a serious concern. This is of particular concern to vectors that integrate into the DNA, such as retroviral vectors and AAV vectors.

Expedited reporting to the regulatory authorities of serious adverse events observed during a clinical trial is an important feature of clinical trial conduct that has been simplified as a result of the Gelsinger incident. Now the adverse event reporting requirements are harmonized such that in all instances, serious, related and unexpected adverse events must be reported to the FDA and OBA, and the timeline for submitting expedited safety reports to the RAC and FDA are identical.

Expedited safety reports should be submitted in a MedWatch form (Form FDA 35001) to both FDA and OBA, or the OBA AE form to OBA. In certain instances, the FDA has mandated that reports of both expected and unexpected adverse events be submitted to IRB and FDA at monthly intervals. These may be instances where the gene therapy product encodes the first gene in its class or the gene therapy product is the first vector in its class to be tested in humans.

The responsibility of who submits the adverse event to the regulatory authority is different among FDA, OBA, IRB and IBC. The investigator must submit expedited safety reports to OBA, IBC, and the IRB. The sponsor (normally the sponsor of a commercial IND) must submit expedited safety reports to the FDA. If the sponsor is also the investigator holding the research IND, then the investigator submits the safety report to the FDA.

During the conduct of the clinical trial, there is a requirement for annual reports to be submitted to FDA and OBA. These reports include updates on progress during the past year of adverse events seen in the clinical trials. In addition, any new information regarding manufacturing and nonclinical studies is summarized in the annual reports.

After Completion of the Clinical Trial

Stemming from the SCID-X1 incident, the FDA has mandated a 15-year follow-up for all subjects in gene therapy clinical trials involving retroviral vectors and other integrating gene therapy vectors. Their new guidance document, *Gene Therapy Clinical Trials–Observing Participants for Delayed Adverse Events–Draft Guidance–August 2005*, lays out a flow chart for determining which gene therapy vectors are subject to the 15-year monitoring. In general, clinical trials utilizing vectors that integrate into the host cell DNA are subject to this monitoring requirement, whereas clinical trials that utilize non-integrating vectors are not subject to this follow-up obligation.

The suggested monitoring consists of annual physical examinations of each subject for the first five years followed by a questionnaire for years 6 – 15. The FDA is particularly concerned about the following events: *de novo* cancer, and neurological, rheumatologic and immunologic/hematologic disorders.

Conclusion

Barriers to the entry of gene therapy products into the U.S. market are currently very high. Gene therapy clinical trials undergo greater regulatory scrutiny than other clinical trials testing investigational drugs and biologics. There must be oversight by both the FDA and the NIH. The sponsor embarking on clinical trials should realize that there are two sets of gene therapy documents to be filed, one for the FDA, and the other for OBA/NIH. In addition, for certain types of gene therapy vectors, there is also the 15-year follow-up requirement for subjects receiving gene therapy.

Outside of the U.S., gene therapy has progressed further. For example, a gene therapy treatment for head and neck tumors (utilizing adenoviral vector encoding the p53 gene) has been approved in China. In addition, a marketing application has been filed in Europe for the treatment of glioma (with adenovirus encoding herpes simplex virus-thymidine kinase gene).[16]

In the United States, despite these regulatory hurdles, there is currently one gene therapy trial in Phase 3 and three in Phase 2b trials. Therefore, there is reason to hope that in the very near future, one of these four gene therapies will be approved and marketed in the U.S. Once the first gene therapy drug is approved, there will be encouragement within biotech and pharmaceutical companies to continue developing the gene therapy technology into future medicines, despite the higher regulatory burdens in the United States.

REFERENCES

1. FDA Gene Therapy Letter, March 6, 2000, http://www.fda.gov/cber/letter.htm.
2. Gene Therapy Patient Tracking System, June 27, 2002, http://www.fda.gov/cber/genetherapy/gttrack.htm.
3. Notice of Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), *Federal Register 2000;* 65: 60327-60332.
4. Human Gene Therapy–Harsh Lessons, High Hopes, *FDA Consumer Magazine* September-October 2000, http://www.fda.gov/fdac/features/2000/500_gene.htm.
5. http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp.
6. http://www.atcc.org/documents/pdf/VR-1516text2.pdf.
7. Hutchins B, Sajadi N, Seaver S, Shepard A, Bauer SR, Simek S, Carson K, Aguilar-Cordova E, 2000. Working towards an adenoviral vector testing standard. *Molecular Therapy*: 2:532-543.
8. Cellular, Tissue and Gene Therapies Advisory Committee, July 13, 2001, http://www.fda.gov/ohrms/dockets/ac/01/slides/3768s1_01_BAUER/index.htm.
9. Biological Response Modifier's Advisory Committee Meeting #30: Adenovirus Titer Measurements and RCA levels, http://www.fda.gov/ohrms/dockets/ac/01/briefing/3768b1_01.pdf.
10. Amendments and Updates to Human Gene Transfer Protocols Recombinant DNA, Recombinant DNA Advisory Committee Meeting, June 28-29, 2000, http://www4.od.nih.gov/oba/rac/amendments/mod600a.htm.
11. AAV Reference Standard Meeting Minutes 6/5/2003, http://www.wilbio.com/ReferenceMaterials/pdfs/AWG03Minutes.pdf.
12. Hacein-Bey-Abina S, et al. LMO-2 associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science* 2003; 302(5644): 415-9.
13. Couzin J, Kaiser J. As Gelsinger Case Ends, Gene Therapy Suffers Another Blow. *Science* 2005; 307:1028.
14. Biological Response Modifier's Advisory Committee Questions, February 28, 2003, http://www.fda.gov/ohrms/dockets/ac/03/questions3924Q2_1.doc.htm.
15. Biological Response Modifier's Advisory Committee Minutes, February 28, 2003, www.fda.gov/ohrms/dockets/ac/03/minutes3924M2.pdf.htm.
16. Branca M. Gene therapy: cursed or inching towards credibility? *Nature Biotech*: 23: 519-521.