

Withdrawal/Redaction Sheet

Clinton Library

DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. letter	Steven Masiello to Jeffrey Isner (10 pages)	05/03/2000	P6/b(6)

COLLECTION:

Clinton Presidential Records
Domestic Policy Council
Devorah Adler
OA/Box Number: 20471

FOLDER TITLE:

Gene Therapy [Folder 4]

2012-0463-S

rc755

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

- P1 National Security Classified Information [(a)(1) of the PRA]
- P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
- P3 Release would violate a Federal statute [(a)(3) of the PRA]
- P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
- P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
- P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).

RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

- b(1) National security classified information [(b)(1) of the FOIA]
- b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
- b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
- b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
- b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
- b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
- b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
- b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]



FACSIMILE

RUSH

DATE: 5.3.00
TO: Deonah / Rachel / Chris J.
FAX#: 456-5557

FROM: Mary Beth Donahue
Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

Deonah. please give copy to Chris and Rachel.
Thank!
Eileen

P.S. Tell all - any questions, call Liz.

Withdrawal/Redaction Marker

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F A C S I M I L E

DATE: 3/3

TO: Chris Jennings / Deborah

FAX#: _____

FROM: Liz Summy
Deputy Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

We'll send you press paper when we have it. This is an internal primer on gene therapy that ASPA put together. We thought it might be of interest

liz

3 Pages [including this cover]

Gene Therapy Research
January 2000

Gene therapy research, like any form of clinical research, can pose both potential benefits and risks to research subjects. Federal policy has sought to preserve the benefits of this research while at the same time protecting against possible abuse or harm to research subjects. Both the FDA and NIH are committed to minimizing the risks and ensuring that patients are fully informed of such risks. Every effort is made to make certain that gene therapy clinical trials are safe and in conformance with Federal guidelines and regulations.

FDA, NIH and other HHS agencies play important roles in overseeing health research and protecting the rights of people enrolled in federally funded clinical trials in general. For gene therapy research, there is also a special NIH panel, the Recombinant Advisory Committee (RAC) that provides oversight and public discussion of gene transfer clinical research.

These agencies work with ethical oversight committees, known as institutional review boards, which are responsible for ensuring that people who agree to participate in studies fully understand the nature of the research and willingly consent to participate. FDA and NIH rely on the IRBs to help ensure that research participants give informed consent and that patients are protected. It is also the responsibility of the sponsor and institution to ensure that they follow all of the conditions spelled out in the gene therapy trial protocol that is approved by the FDA. They have the responsibility to follow this approved protocol to ensure patient protection. If they do not take this responsibility seriously and deviate from the protocol, punitive action can be taken by federal regulators.

While specific guidelines and processes are in place for sponsors and institutions to follow, FDA and NIH are continuously working to strengthen these processes and make sure all parties are fully informed. In this regard, the Agencies have taken the following steps to ensure that gene therapy clinical trials are safe and in conformance with Federal guidelines and regulations:

- * NIH Guidelines clearly place the responsibility for reporting all serious adverse events on the investigator and on the institution. In addition, all investigators who register a protocol with the NIH receive a letter from NIH reminding them of their obligations under the Guidelines. Nonetheless, in November 1999, NIH issued a memorandum asking all institutions conducting human gene transfer research to review their institutional policies and procedures to ensure compliance with the NIH Guidelines. The memorandum was sent to all units that have responsibility for protection of human subjects at the institutions conducting human gene transfer studies.

- * FDA and NIH have strengthened their processes to share information by implementing two new Standard Operating Procedures and Policies (SOPP) whereby FDA will notify NIH about adverse events and any other changes in gene therapy protocols on a weekly basis, enhancing each Agency's monitoring capabilities.

- * A working group reporting to the NIH Director was established to comprehensively

review in public session the role of NIH in gene therapy clinical trial oversight including making recommendations regarding reporting, analysis and public disclosure of serious adverse events.

- * NIH is working on developing an interactive web-based database to ensure public access to data on gene transfer research.

- * The NIH Office of Extramural Research will undertake a series of site visits to NIH funded institutions to ensure that there is understanding of the NIH Guidelines.

- * Both FDA and NIH will continue to sponsor or co-sponsor educational outreach programs to ensure that all parties understand guidelines and regulations concerning gene therapy clinical trials.

- * FDA plans to issue a proposed rule on the public disclosure of information regarding gene therapy clinical trials that would provide more information on these trials to the general public.

- * FDA is enhancing regulatory research to improve product safety.

- * FDA has provided guidance documents to industry and other interested parties on gene therapy products and will take action to build upon existing guidance.

- * FDA will conduct more inspections to increase oversight of gene therapy INDs.

Proposal Regarding Appropriate Regulation of Gene Therapy Research

- Recent reports of possible errors or failures in reporting adverse events to NIH or in properly informing research participants about the risks and benefits of the research have led some to question gene therapy studies.
- We must act decisively both to restore public confidence in gene therapy research and to ensure that as this important research moves forward, we provide appropriate oversight and solid patient safeguards.
- Gene therapy research offers tremendous promise for patients – treatments for heart disease and cancer, the two most common causes of premature death in America; treatment of birth defects before they cause lifelong disability; treatments or cures for devastating (and often fatal) genetic disorders; and many others we cannot even envision today.
- NIH's work on mapping the human genome will provide researchers with the knowledge and understanding to accomplish even more.
- We must do everything we can to enhance the promise of gene therapy research with substantial protection of patients who participate in gene therapy clinical studies. Toward this end, I am announcing the following initiatives and directing prompt implementation by Secretary Shalala.
 1. The Department of Health and Human Services will immediately prepare a written report describing the number and nature of serious adverse event (SAE) reports that have been received by the National Institutes of Health (NIH) and/or the Food and Drug Administration (FDA). Specifically, this report is to state how many NIH-reported SAEs were expected to occur as a result of the progression of the patient's illness and how many were unexpected. The report will further indicate how many of the unexpected SAEs – which the law requires to be immediately reported to the FDA if they took place after the treatment was administered – were indeed reported in accordance with this requirement. The report will provide an analysis of how many of these unexpected adverse events were possibly or probably caused by the use of a gene therapy product, as well as the number of such product-caused events that resulted in death. It is critical that the public record be made clear as to these matters.
 2. The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) will take immediate steps to harmonize their reporting requirements for serious adverse events. In the future, there should be no confusion caused by inconsistent reporting requirements. Instead, both agencies will simultaneously receive identical reports containing identical information. FDA's safety reporting regulations serve as a model for harmonizing such reporting requirements.
 3. The Department will establish a Gene Therapy Data Analysis Task Force, under the direction of FDA. The task force will be comprised of FDA and NIH gene therapy experts, medical reviewers, statisticians, and other scientists to review all SAE reports relating to gene therapy clinical trials. The task force will aggregate

and analyze these data, identify relevant trends, and provide periodic reports of their findings to the NIH RAC and the public.

4. NIH will design, in consultation with FDA and the NIH Recombinant DNA Advisory Committee, an investigator training program to enhance professionalism in the conduct of gene therapy clinical research. The training program shall be designed to enhance investigator understanding and compliance with informed consent, adverse event reporting, and elements of gene therapy clinical research. Training will be available on a voluntary basis to both publicly and privately-funded gene therapy investigators. Following an appropriate phase-in period, NIH will require completion of this training program as a condition of an investigator's eligibility for an NIH grant supporting gene therapy clinical research
5. NIH will establish a gene therapy patient information website and hot line to provide prospective, current, and former clinical trial enrollees with information and assistance to evaluate clinical trial participation.
6. FDA will immediately establish a new Office for Cell and Gene Therapies (OCGT) to enhance the Agency's effectiveness in overseeing the conduct of gene therapy clinical trials. FDA's gene therapy expertise is widely respected, while its authority is both comprehensive and unquestioned. All that is lacking is the necessary priority, focus, visibility, and resources without which they cannot assure that gene therapy studies are performed at the highest professional standards. The new Office for Cell and Gene Therapies will provide the necessary leadership and will receive the necessary resources.

- I intend to move swiftly on this crucially important matter. My staff and I will work closely with Secretary Shalala, NIH Acting Director Kirschstein, and FDA Commissioner Henney to implement these policies, which will enhance patient protection while protecting the future of this exciting new technology.

\$ can you ask them to send us examples of consent forms? \$



FAX TRANSMISSION

U.S. Department of Health and Human Services
Office of the Secretary

DATE: 2/28
TO: Devorah Adler
FAX: 456-5557 PHONE: _____
FROM: D. McHugh
Press Office, OASPA
Phone: (202) 690-6343
Fax: (202) 690-6247

TOTAL NUMBER OF PAGES TRANSMITTED: 3

COMMENTS:



NIH NEWS RELEASE

NATIONAL INSTITUTES OF HEALTH

HOLD FOR RELEASE ON
12:01 a.m., February 29, 2000

National Library of Medicine

CONTACT: Robert Mehnert or Kathy Cravedi
(301) 496-6308

NATIONAL INSTITUTES OF HEALTH LAUNCHES "CLINICALTRIALS.GOV"

DATABASE GIVES PUBLIC EASY ACCESS TO INFORMATION ABOUT RESEARCH STUDIES

(BETHESDA, MD) – The National Institutes of Health today announced the launch of the first phase of a consumer-friendly database, *ClinicalTrials.gov*, with information on more than 4,000 federal and private medical studies involving patients and others at more than 47,000 locations nationwide. The new database may be reached at <http://clinicaltrials.gov/>.

Clinical trials are medical research studies that seek to evaluate the safety and effectiveness of new drugs, medical procedures, or other means of treating, diagnosing, or preventing diseases. This type of research helps investigators learn how different people respond to medications or other therapeutic approaches, and such investigations may lead to new or improved treatments. Trials are conducted when there is no proven treatment for a specific disease, or to test which treatment works best for a particular disease or condition.

ClinicalTrials.gov provides patients, families and members of the public easy access to information about the location of clinical trials, their design and purpose, criteria for participation, and, in many cases, further information about the disease and treatment under study. There are also contact points for individuals responsible for recruiting participants for each study.

Acting NIH Director Ruth L. Kirschstein, M.D., said, "Through this new database, NIH offers up-to-date information on promising patient-oriented research on hundreds of diseases and conditions. Most of the 4,000 clinical trials now in the database are funded by NIH Institutes and Centers, and result from a long, fruitful partnership between NIH and the American people who support and participate in our work."

"If we are to continue making the giant strides in diagnosis, treatment, and cure of illness that marked the last century, we must have active participation in clinical trials by well-informed volunteers," said Donald A.B. Lindberg, M.D., Director of NIH's National Library of Medicine, which developed and administers the new database. "*ClinicalTrials.gov* is a resource that will benefit trial participants, researchers, health care professionals and, over time, the general public."

(more)

-2-

Dr. Lindberg noted that *ClinicalTrials.gov* may also be reached through the National Library of Medicine's Web site at <http://www.nlm.nih.gov> and through its consumer health information service, MEDLINEplus at <http://medlineplus.gov>. MEDLINEplus has extensive links to information about 350 diseases and health conditions, much of it from the NIH Institutes and Centers.

ClinicalTrials.gov grew out of 1997 legislation that required the Department of Health and Human Services, through the NIH, to broaden the public's access to information about clinical trials on a wide range of diseases by establishing a registry for both federally and privately funded trials "on drugs for serious or life-threatening diseases and conditions." (Section 113, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases," Food and Drug Administration Modernization Act of 1997, Public Law 105-115.)

"The project is proceeding in several major phases," noted Alexa T. McCray, Ph.D., who directs the *ClinicalTrials.gov* project at the National Library of Medicine. "In the first phase we were interested in collecting information primarily about studies that are being funded by NIH, or that are being conducted right here on the NIH campus. With the release of *ClinicalTrials.gov*, the first phase is well under way. In the next phase we will include non-NIH sponsored trials from other Federal agencies and private industry."

ClinicalTrials.gov is a completely confidential Web site. No registration or personal identification of any kind is required. People who search the site will not be contacted by the sponsors of clinical trials or by anyone else.

#

Note: Background information about clinical trials and specific information about the new database is available. The information, in the form of a "Q&A" document, may be requested by email from publicinfo@nlm.nih.gov or by phone from 301-496-6308. It is also linked to this press release on the Web at <http://www.nlm.nih.gov/nn.html>.

NLM also has a listing of current and past clinical trial participants who are available to discuss their experience in locating and participating in a medical study, and statements of support from consumer health organizations such as the American Cancer Society and the American Liver Foundation. These are available by calling 301-496-6308.

<http://clinicaltrials.gov>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Chief of Staff

Washington, D.C. 20201

FACSIMILE

DATE: _____

TO: C. Jennings-

FAX#: _____

FROM: Mary Beth Donahue
Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

Thanks for not
distributing. Final
public Q+A can be
available
tomorrow.

Pages [including this cover]

CLOSE HOLD/CONFIDENTIAL—FOR INTERNAL USE ONLY

[draft 2/10/00 5:30 pm]

QUESTIONS AND ANSWERS

What did St. Jude Children's Research Hospital report to FDA?

On Friday, February 4, St. Jude Children's Research Hospital telephoned FDA to report that a gene transfer vector used in a clinical study of children with cancer may have been contaminated with HIV-1 and hepatitis C (HCV) virus. St. Jude's also informed NIH of the possible contamination.

FDA wants to emphasize that St. Jude's reported a preliminary finding, and that it is likely to be a false positive. Although this test result remains unconfirmed, FDA is taking it very seriously. Specific tests are currently being done to determine whether this test result is valid or is a false positive.

This situation is analogous to the screening of potential blood donors for infectious diseases. When a blood donor's screening test comes back positive, an additional test (called a confirmatory test) must be performed to determine whether the initial result was valid.

What is FDA doing about this report?

FDA's overriding concern in any situation like this one is to protect patients. FDA took or is taking the following actions:

- FDA immediately placed the trials on clinical hold.
- FDA is testing the implicated material to determine whether it is in fact contaminated.
- Working together, FDA and NIH have mapped out a comprehensive strategy for investigating what happened with this clinical trial and taking all the appropriate actions to ensure that patients are informed and protected.

FDA immediately placed a clinical hold on this trial at St. Jude's as well as a similar trial at Baylor University in Houston, where a former St. Jude's researcher was conducting a similar clinical trial using some of the same material used at St. Jude's.

FDA is currently conducting more specific tests on the viral stock preparation from which the viral vector was manufactured. FDA is also asking St. Jude's to have its testing repeated and to conduct additional testing.

The purpose of this testing is to determine whether the initial test result from St. Jude's represents a signal that the viral stock preparation is actually contaminated. Such a signal would represent a fingerprint of the virus but would not indicate whether infectious material is actually present.

If such a signal is found, further testing would be done to determine if the complete virus is present and capable of infecting a patient.

Why didn't FDA immediately go public with this information on February 4?

It's important to emphasize that the St. Jude's findings are preliminary and not confirmed. As a public health agency, FDA did not want to alarm patients and their families unnecessarily.

In addition, because FDA put the research on clinical hold, no new or current patients would be exposed to the material in question.

How many children are potentially involved?

On the basis of the information the institutions have submitted to FDA so far, approximately twenty children with cancer have participated in the clinical trials at St. Jude's and at Baylor over the past two-and-one-half to three years. Unfortunately, only six of those patients are alive today.

How long ago was the last treatment given in this trial?

Two children received this experimental therapy last week.

What caused the deaths of those patients?

FDA is focusing considerable attention on the clinical records of all the patients enrolled in these trials. At this point, our analyses is that the deaths are due to progression of the disease, neuroblastoma or acute leukemia. However, it is important to remember that most patients enrolled in gene therapy trials have serious, life-threatening diseases, and in many cases, have exhausted other available treatment options. Many of these patients die from causes related to their underlying disease, and in particular, children with neuroblastoma and acute leukemia have exceptionally virulent disease with corresponding short life expectancy.

How long will it take to get the autopsy reports?

When patients who are enrolled in a clinical trial die, the decision about an autopsy rests, of course, with the family. Any autopsy reports would be required to be submitted to FDA as part of its investigation

Since this trial involved gene therapy, was NIH notified?

As always, FDA and NIH are working closely together to protect patients in clinical trials. This trial was not funded by NIH. FDA did notify NIH immediately after learning about the possible contamination on Friday, February 4. We have mapped out a comprehensive strategy for dealing with this issue, which includes obtaining test results, investigating the clinical trials, looking into the Institutional Review Boards responsible for protecting human research subjects, and preparing to communicate with the families of the research subjects. Our close collaboration will continue.

Is this the same kind of study that was stopped at the University of Pennsylvania?

This study used the same gene transfer vector (an adenovirus) as was used in the gene transfer trials at the University of Pennsylvania. In this case, however, FDA issued a clinical hold on the St. Jude's trial because of the possibility that the manufacturing of the vector may have been compromised during production. The concern here stems not from an adverse reaction in a patient, as in the case of the University of Pennsylvania trial, but because the vector is potentially contaminated.

Does NIH have a role?

Yes. The Office for Protection from Research Risks (OPRR), part of NIH, has contacted St. Jude Children's Research Hospital, directing them to follow up on the informed consent process for this clinical trial--that is, to be prepared to share information about the possibility of contaminated adenoviral vectors used in this research--and their potential risks--with the parents of the children in the trial.

The Office for Protection from Research Risks visited St. Jude's in November 1999. Why didn't OPRR find out about this then?

OPRR staff visited St. Jude's in November 1999 to address an unrelated clinical study. No information about the possible contamination in the gene transfer trial was given to OPRR at that time. St. Jude's informed the FDA about this trial on February 4, and FDA immediately contacted NIH, which then contacted OPRR.

Have the parents of these children been notified about this finding?

FDA and NIH are very concerned about the potential impact of this news on the parents and families involved, and want to ensure that they are informed as quickly as possible. As with any laboratory test, a positive finding from an

initial general test that a substance may be contaminated must be repeated with more specific tests to determine if the initial results are accurate.

In such cases, it is the responsibility of the institution conducting the clinical trial to notify the families. A member of the research team who has the closest relationship with the family, e.g., the principal investigator, is expected to notify them about the finding.

Should these children be tested for HIV-1 and HCV infection? Should the caregivers of these children be tested?

Certainly, it is up to individuals to decide whether to be tested. But because at this point there is only the potential that the viral vector was contaminated, FDA does not see an immediate need for testing.

If the testing shows that the viral vector is both positive and infectious, then the children and their parents and other caregivers in the home care setting would need to be tested.

Caregivers in hospital settings would not require testing, because of the universal precautions against HIV and other infections in place at the nation's hospitals. However, anyone concerned about the potential for infection should seek testing.

How long will it take to test the material for contamination?

FDA is moving as quickly as possible to obtain and test the material, but these tests cannot be done overnight. Initial test results should be available in a few days, but it is likely to be ten days to two weeks before we have a definitive answer.

If the initial test results are negative, then the material will be tested several times more just to be sure the initial results are accurate.

If the initial test results are positive, then further testing will be conducted to determine whether the viral material present is actually infectious. This would be done by genetic sequencing. Tissue culture and animal studies would be performed to determine infectivity.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

February 1, 2000

The Honorable Henry A. Waxman
House of Representatives
Washington, D.C. 20515

Dear Mr. Waxman:

I am writing to address additional questions raised in your January 10 letter about the oversight by the National Institutes of Health (NIH) of clinical gene transfer protocols. Your questions are in follow up to your previous inquiry.

First and foremost, let me assure you that I certainly concur that the NIH must take immediate steps to ensure that our oversight of gene transfer research is exemplary. In our earlier correspondence, we outlined a number of steps we are taking to address problems, and we will continue to keep you apprised of our progress.

With regard to the NIH's oversight of gene transfer research, the NIH is convening a working group of the Advisory Committee to the Director, NIH, to examine the current NIH framework for oversight and public discussion of clinical gene transfer research, especially with regard to the roles of the Recombinant DNA Advisory Committee (RAC) and the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. The working group is being asked to examine several options for NIH oversight, and among them is re-establishing RAC approval of novel protocols. The working group will be holding its first meeting next month, and it will meet again in March in conjunction with the RAC. We hope to receive final recommendations from the working group in May.

An important component of oversight is knowledge of the potential safety concerns associated with gene transfer research. In this regard, and as discussed in further detail below, the RAC is expected to discuss its recommendations regarding NIH requirements for serious adverse event reporting at its next meeting in March.

The NIH is committed to its oversight responsibilities in gene transfer research. To this end, the Office of Biotechnology Activities (OBA) (formerly the Office of Recombinant DNA Activities) has, and has had, the necessary resources to conduct its present responsibilities, and will receive any additional resources required to meet any new or expanded responsibilities. For example, recently, the OBA has taken on responsibility for two Secretarial-level committees on genetic testing and xenotransplantation. Contrary to press reports, OBA's budget and personnel increased significantly attendant to these new responsibilities. In addition, as the field of gene transfer has grown in the last few years, the

Page 2 - The Honorable Henry A. Waxman

OBA budget and personnel have grown concomitantly. The OBA is currently recruiting additional staff to enhance management of clinical protocol submissions, amendments, and annual reports; analysis of serious adverse event reports; review of vector safety issues; educational programs for gene transfer research investigators; and database management.

With regard to NIH's responsibility to ensure public access to data on gene transfer research, the NIH has been working diligently to develop an interactive web-based database. The database is designed to enable users to search for specific variables, analyze aggregate data, and identify emerging trends in gene transfer research. This task has proven to be difficult and highly complex, particularly in light of the multiple audiences that are expected to use this resource. Our goal is to develop an electronic resource that both the general public and the scientific community will be able to easily access and use to obtain current information about specific protocols, including information about adverse events and developments in gene transfer research. The first phase of the database will be publicly available by the end of this year. In subsequent years, we will evaluate the first phase of the database and, as necessary, refine elements which do not meet user expectations.

It is, however, important to emphasize that all of these data, including adverse event reports, are made available in the public domain, once they have been received to the NIH. Comprehensive information on all human gene transfer trials registered with the NIH since the inception of the *NIH Guidelines* is now, and always has been, publicly available. At each RAC meeting, a portion of the agenda is devoted to the presentation of clinical gene transfer trials that have been registered with the NIH, as well as a presentation of any serious adverse events that have been reported since the previous meeting. A copy of each new proposal is available to the public at all times. In fact, the NIH provides a copy of any proposal submitted to the NIH upon request by an investigator or by a member of the public. In addition, information on gene transfer protocols and data reviewed at each RAC meeting are posted on NIH's Web site, <http://www.nih.gov/od/oba/>. This includes discussions of novel protocols, a list of registered protocols, core information about each protocol--elements such as the protocol title, trial site, principal investigator, disease under study, and vector being used for the gene transfer--and any reported serious adverse events.

You also asked me to comment on the failure of investigators doing clinical gene transfer to comply with requirements for reporting all serious adverse events to the NIH and to provide additional information about the causes of these events. Like you, we are deeply concerned about the under-reporting of serious adverse events to the NIH, and we are taking steps to address this problem expeditiously.

The *NIH Guidelines* clearly place the responsibility for reporting all serious adverse events on the investigator and on the institution. In addition, all investigators who register a protocol with the NIH receive a letter from the NIH reminding them of their obligations under the *NIH Guidelines* to report all serious adverse events. Even though these reminders are explicit and

Page 3 - The Honorable Henry A. Waxman

targeted to each investigator, they clearly have not accomplished what we intended. The failure of investigators and institutions to comply with this requirement must be shared by the NIH itself. We were receiving only a small number of adverse event reports and we certainly should have recognized this as a sign of under-reporting.

Why have investigators failed to report serious adverse events and what are we doing to ensure future compliance with the *NIH Guidelines*? Despite the clearly stated NIH requirements for adverse event reporting in the *Guidelines*, we believe that non-compliance was, at least to some extent, the result of confusion on the part of many investigators and institutions regarding the significant differences between the NIH and the FDA requirements. Nevertheless, while this is an explanation for inadequate reporting, it is not an excuse. We must be sure that this does not happen again. Greater efforts to ensure that investigators and institutions are cognizant of their responsibilities are clearly needed, and the NIH is dedicating additional resources to educating both about their responsibilities and obligations under the *NIH Guidelines*.

According to the *Guidelines*, as a result of non-compliance, the NIH can suspend, limit or terminate NIH funds for a particular gene transfer project or for all recombinant DNA research at an institution. The NIH can choose to impose a requirement for prior NIH approval of any or all recombinant DNA projects at an institution. We can also conduct site visits to ensure that institutions have the proper processes in place to comply with the *Guidelines*. To this end, the NIH Office of Extramural Research will undertake a series of site visits to NIH funded institutions to assess the level of understanding of NIH rules and to identify any problems associated with NIH oversight, paying particular attention to compliance with the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, as well as to financial conflicts of interest.

We have taken several immediate steps. First, we sent a memorandum to institutions conducting human gene transfer research directing them to review their institutional policies and procedures for ensuring compliance with the *NIH Guidelines* and requested that any institution that found compliance problems notify the NIH. A copy of the memorandum was sent to Institutional Review Boards, Institutional Biosafety Committees, and principal investigators at institutions conducting human gene transfer studies. We are in the process of reviewing responses to the memorandum and are following up with institutions, as necessary.

Second, the FDA established a new process for sharing information with NIH and notified the gene transfer research community of this change in a November 5, 1999, letter. The FDA formalized the process in two new Standard Operating Procedures and Policies (SOPPs). The SOPPs, which were issued December 7, 1999, institute weekly notification to NIH of reports of adverse events and any other changes in gene therapy protocols received by the FDA. While these new SOPPs will enhance the ability of NIH to monitor serious adverse

Page 4 - The Honorable Henry A. Waxman

events, in no way will they diminish the responsibility of investigators to fulfill their reporting requirements to NIH.

Third, a working group of the RAC is reassessing the current requirements for the scope and timing reporting of adverse events to the NIH, especially with respect to the current differences between the adverse event reporting requirements of the NIH and the FDA. The working group proposal will be discussed at the next RAC meeting in early March.

Fourth, the NIH, with concurrence from the RAC, is taking steps to prevent sponsors from circumventing public access to adverse event reports by labeling this information proprietary. The RAC articulated its strong objection to this practice, highlighted the importance of ensuring patient confidentiality to the greatest extent possible, and recommended changes in the *NIH Guidelines* to ensure public access to adverse event reports.

Finally, in regard to whether the change in the approval function of the RAC contributed to the under-reporting problem, it is important to point out that the RAC's role in protocol approval has no bearing whatsoever on the obligation of investigators and institutions receiving NIH funds for recombinant DNA research to comply with the clearly stated reporting requirements set forth in the *NIH Guidelines*.

You also asked to have an update on NIH's investigation of the circumstances of the issuance of the May 14, 1996, letter. Because of the seriousness of this matter, we have referred it to the Office of the Inspector General in the Department of Health and Human Services for further review. Of note, between May 1996 and October 1997, the review and approval of protocols deemed novel by the RAC did not change.

Finally, you also requested that I comment on whether the public interest would be better served by moving the RAC and OBA to the Office of the Secretary (OS), similar to the transfer of the Office for Protection from Research Risks (OPRR). The NIH agreed that the transfer of OPRR to the OS was appropriate. There are significant differences, however, in the roles and responsibilities of OBA, the RAC, and OPRR and, therefore, important reasons for the RAC to remain within the NIH umbrella. The *NIH Guidelines* govern not only investigators who receive NIH funding for gene transfer research, but also investigators conducting gene transfer research at institutions that receive funding from NIH to perform research involving recombinant DNA. Public accountability via the *NIH Guidelines* is a result of NIH funding, which provides a direct enforcement authority. The authority to enforce compliance with the *NIH Guidelines* should remain connected to the funding entity. Most importantly, gene transfer research is highly experimental and must remain close to the science enterprise and those who administer it. OBA benefits by being closely connected to the research activities of the NIH, since NIH staff help keep OBA and the RAC apprised of emerging scientific developments, provide input into the development of agendas for scientific conferences, and identify issues for RAC consideration. Finally, one of the

Page 5 - The Honorable Henry A. Waxman

principal reasons for locating OPRR outside the NIH was to strengthen its ability to interact with other agencies within DHHS and with other Departments. In the case of gene therapy studies, NIH has a strong working relationship with the FDA and, in response to specific problems regarding under-reporting of adverse events, new procedures have been instituted to further enhance interagency communication. Moreover, FDA and other governmental agencies are represented on the RAC.

Thank you for your continuing interest in our efforts to ensure that NIH's oversight role in gene transfer research is effective and appropriate. We welcome your interest and appreciate your continued support of our efforts. We will keep you apprised of our progress.

Sincerely,

/s/

Ruth L. Kirschstein, M.D.
Acting Director

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January 27, 2000, Thursday
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Teenager's Death Is Shaking Up Field of Human Gene-Therapy Experiments

By SHERYL GAY STOLBERG

Perhaps no event in recent medical history has done more to shine light on the inherent conflict of interest between researchers and their subjects than the death of an 18-year-old from Tucson in a **gene therapy** experiment at the University of Pennsylvania.

It has been four months since Paul Gelsinger made the wrenching decision to withdraw life support from his son, Jesse, after an infusion of **gene**-altered viruses meant to correct an enzyme deficiency caused an immune response that spiraled out of control. The grieving father then vowed to stand by the Pennsylvania scientists "until my dying day."

Now, amid accusations by the Food and Drug Administration that the researchers repeatedly ignored rules intended to protect patients from harm, Mr. Gelsinger has hired a lawyer. He says he was told too little when he encouraged his son to volunteer for the study, which offered no benefit to the teenager, but was designed to test the safety of a treatment for babies with a fatal form of his disorder.

The case may lead to increased regulation of clinical trials in **gene therapy** research, a 10-year-old field that is already heavily scrutinized. And it shows how expectations diverge in early-stage clinical trials, when researchers want to learn if cutting-edge treatments are safe, but patients are hoping for a cure.

On Friday, the drug agency shut down all human **gene therapy** experiments at Penn after finding "numerous serious deficiencies" in the way the clinical trial involving the younger Mr. Gelsinger was run. The agency did not attribute the youth's death to lapses by university doctors.

But Dr. Kathryn Zoon, who runs the agency's Center for Biologics Evaluation and Research, said in an interview on Tuesday that agency officials were considering policy changes as a result of the Gelsinger case. She said the agency was thinking of imposing a new rule that would allow it to make public more information about **gene therapy**. And it is also considering beginning random inspections of clinical trials of the sort it conducted at Penn.

At the National Institutes of Health, officials are re-examining the role of the Recombinant DNA Advisory Committee, which oversees **gene therapy** research but lost much of its authority in a reorganization four years ago. Congress is also considering stepping in. Next week, a Senate subcommittee

will hold a hearing on whether there is sufficient oversight for **gene therapy**.

Dr. James Wilson, who directs Penn's Institute for Human **Gene Therapy**, declined an invitation to testify, and declined to be interviewed for this article.

Mr. Gelsinger, who is on the witness list, says he and his son had no idea there were risks -- of hepatitis, liver damage, and even a remote chance of death. Neither did they know, he says, that despite 300 clinical trials, **gene therapy** had never cured anyone. He said they were lulled into participating by the idea that the study might prove that the **therapy** his son was receiving might work on his disease.

"I would have liked to have had somebody there who was not affiliated with Penn that could have assisted in describing the whole process of **gene therapy**," Mr. Gelsinger, who works as a handyman, said in a telephone interview from his Tucson home. "I didn't research it. But I shouldn't have to research it. I believed these guys, everything they were telling me."

As scientists map the human genome, they are uncovering mutations for genetic disorders -- including ornithine transcarbamylase (OTC) deficiency, from which Jesse Gelsinger suffered -- at a rapid pace. The idea of **gene therapy** is that these illnesses can be cured, or prevented, through an infusion of corrective genes. Typically, the genes are encased in a virus that acts as a taxicab, of sorts, to deliver them to the proper cells in the body.

One issue of particular concern to regulators about the Gelsinger case is the process of informed consent. Federal rules require that the risks and benefits of an experiment be explained to patients in understandable language, and that patients be given sufficient time to make the decision. And if some patients experience serious side effects, all volunteers are supposed to be informed and then must consent again.

These requirements were not met in the Penn study, the drug agency says. The informed consent form the Gelsingers reviewed omitted information about monkeys that had died after being given a similar, though stronger, treatment. And when patients experienced elevations in liver enzymes that were significant enough to bring a halt to the trial, the drug agency was not notified, and the consent form was not revised.

Some worry that biotechnology money is altering the informed consent equation. At Penn, for instance, Dr. Wilson also founded a biotechnology firm, Genovo, in which he holds stock. Although the company did not sponsor the study in which Jesse Gelsinger participated, it does provide financial backing for Dr. Wilson's institute. In previous interviews, Dr. Wilson has said Penn had rules to prevent a conflict of interest between his academic position and his ties to the company.

But Dr. Ruth Macklin, a bioethicist on the National Institutes of Health advisory committee, said, "There is one feature of this field that is quite different from general run-of-the-mill research, and that is that large numbers of the researchers themselves have a financial stake."

Lapses in informed consent are common, said Dr. Gary B. Ellis, director of the federal Office for Protection From Research Risks, which investigates reports of abuses. Dr. Ellis says more than 90 percent of the cases he looks at reveal problems with informed consent, a figure that does not surprise ethics experts.

"Consent forms are often very deficient and they overpromise," said Dr. LeRoy Walters, a bioethics professor at Georgetown University and former chairman of the Recombinant DNA Advisory Committee at the N.I.H. "They make Phase One studies" -- safety tests -- "sound like the cure for your cancer."

Even when the forms are clear, and accurate, Dr. Walters and others say, the discussions doctors have with their patients may cloud the issues. Patients anxious for a cure may engage in a kind of selective hearing, taking in only to information about potential benefits, while researchers eager to sign up study volunteers may gloss over the risks.

A conversation with Mr. Gelsinger reveals just how cloudy, and fraught with emotion, the informed consent process can become. When he learned late last year that the information about the monkeys had been omitted from the consent form, he said, "I was willing to overlook it."

But as he reflects on his decision making process, he said, he keeps coming back to a talk he had with Dr. Mark Batshaw, a principal investigator in the study. He said Dr. Batshaw told him the treatment was already working in some patients and that because of the particular nature of his disorder, Jesse Gelsinger would allow the scientists to "show exactly how well this works."

Dr. Batshaw, through a spokeswoman, said the Gelsingers were never told the **therapy** could be considered a treatment. Still, Mr. Gelsinger says he feels misled. "They wanted to lock Jesse in," he said. "They didn't want him backing out."

The experiment involving Mr. Gelsinger was unusual, as **gene therapy** research goes, because the participants were not particularly sick. Some were carriers of the **gene** for OTC deficiency, a disorder in which the liver cannot process ammonia, a toxic breakdown product of food. Others, like Mr. Gelsinger, suffered from a mild form of the disease; in Mr. Gelsinger's case, it was controlled through diet and drugs.

The **therapy** involved an infusion of trillions of particles of the OTC **gene**, encased in a weakened cold virus, adenovirus. When the drug agency investigated, it said Mr. Gelsinger should never have been treated, because his liver was not functioning well enough before doctors gave him the infusion.

The findings have given a boost to those pressing for greater openness in the field. The Recombinant DNA Advisory Committee, known as "the RAC," which operates in public, is supposed to monitor patient safety, but in practice that job has been left to the drug agency, which is required by law to do its work in secret.

Mr. Gelsinger, for instance, said he did not even know the RAC existed until after his son's death, when he learned that the panel had reviewed the experiment, and that some members thought it was too risky.

Yet, critical though he is of Dr. Wilson's group, he still says he wants their work to go forward. He is troubled that other **gene therapy** researchers appear to be backing away from Dr. Wilson.

"They'll sacrifice Penn, they'll sacrifice Jim Wilson," Mr. Gelsinger said. "These guys screwed up, yes. But they should not be put out of business. They should be able to lick their wounds and go back to work, because guess what? They'll be clean from now on."

Correction: January 28, 2000, Friday

Because of an editing error, an article yesterday about problems with gene therapy experiments, especially one at the University of Pennsylvania, referred incorrectly to information given to one research subject, Jesse Gelsinger, and his father, Paul Gelsinger. Far from having being unaware that the experiment was risky, Paul Gelsinger said, they knew there were serious risks, including risks of hepatitis, liver damage and even death.

Organizations mentioned in this article:

University of Pennsylvania

Related Terms:

Medicine and Health; Genetics and Heredity; Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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Q and A - Gene Therapy
January 31, 1999

Q. Why didn't NIH know about the deaths reported today in the Washington Post re gene therapy trials?

A.

* Under the NIH guidelines, it is the responsibility of the investigator and the institution conducting the trial to report all serious adverse events to the NIH. NIH relies on these parties to take their responsibilities seriously and report all necessary information.

* Even though NIH sends explicit reminders to investigators to report serious adverse events, both NIH and FDA are exploring additional steps to prevent non-reporting from happening in the future.

Q. What steps are being taken?

* Gene therapy trials, like all clinical trials, pose both great promise and potential risks. NIH takes very seriously its role to promote and protect patient safety to the best of its ability and is looking at ways to further strengthen reporting systems.

* NIH and FDA has established a new notification process for serious adverse events whereby FDA notifies the NIH when it receives serious adverse event reports from investigators and sponsors. NIH can thereby verify whether it has received the same reports and, if not, follow up with investigators.

* In November 1999, NIH issued a memorandum asking all institutions conducting human gene transfer research to review their policies and procedures to ensure compliance with the NIH Guidelines.

* NIH and its advisory committee on these issues are considering changes to the NIH Guidelines about the scope and time frame of reporting.

* A working group has been formed to thoroughly review the role of NIH in oversight of gene therapy and make specific recommendations including the NIH role in regard to reporting, analysis and public discussion of serious adverse events.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Chief of Staff

Washington, D.C. 20201

FACSIMILE

DATE:

1/24/00

TO:

W. EVORAH

FAX#:

FROM: Mary Beth Donahue
Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

8 Pages [including this cover]

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NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: James M. Wilson, M.D.		PERIOD OF INSPECTION See page 7	C. F. NUMBER 2531753	
TITLE OF INDIVIDUAL Director Institute for Human Gene Therapy		TYPE ESTABLISHMENT INSPECTED Sponsor/Investigator		
FIRM NAME University of Pennsylvania Health System		NAME OF FIRM, BRANCH OR UNIT INSPECTED James M. Wilson, M.D.		
STREET ADDRESS 204 Wistar Institute, 3601 Spruce Street		STREET ADDRESS OF PREMISES INSPECTED Same		
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The following observations relate to the clinical study
"Recombinant Adenovirus Gene Transfer in Adults with Partial
Ornithine Transcarbamylase Deficiency (OTCD)":

1 - The sponsor/investigator did not submit protocol version 1
[REDACTED], and both of the version 4 protocols (July
1998, and November 1, 1998 - last version) to the Food and Drug
Administration (FDA).

2 - The sponsor/investigator admitted all of the 18 patients
[REDACTED] into the study without prospectively documenting
that all eligibility criteria were met.

3 - The sponsor/investigator developed a patient eligibility
form in the fall of 1999, after the study was placed on
clinical hold. None of the OTCD patient eligibility criteria
forms were signed and dated to show who completed them.

4 - The serum [REDACTED] level inclusion criterion was changed
from [REDACTED] in the original protocol version (version
1) to [REDACTED] in the subsequent version of the protocol
(version 2) without the approval of the Institutional Review
Board (IRB) or the FDA. This change was not documented in the
summary of changes in protocol version 2 (August 1997).

5 - Patient [REDACTED] was enrolled in the study even though [REDACTED]
did not meet the eligibility criteria. The patient's plasma
[REDACTED] levels were in the range of [REDACTED] to [REDACTED]
during the hospitalization period before the study drug was
administered. The protocol specified that patients must have
plasma [REDACTED] levels [REDACTED] prior to infusion of the
study drug. Although this patient met this criterion during

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(Nov. 4, 96)

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screening three months earlier, this criterion was no longer met during the period immediately before infusion of the study drug. 6 - The sponsor/investigator does not have a standard operating procedure (SOP) to conduct a clinical study. The sponsor did not monitor the OTCD study to assure and confirm that the participating investigators fulfilled the following responsibilities: performance of all protocol-required testing, maintenance of complete and accurate records, complete and timely communications with the IRB including protocol revisions and adverse event reports, and that the informed consent was properly executed. 7 - The sponsor/investigator did not incorporate the FDA's request to amend the protocol ~~of male patients per cohort to~~ and always have him to be the ~~patient~~ and did not forward the change to the IRB. 8 - Patient ~~, a male patient,~~ was allowed to enter the study as the ~~patient in cohort~~ without the approval of the FDA. 9 - The consent process was not well documented for 9 of 18 patients enrolled in the study, as reflected in this item and in item 10, below: <del></del> <i>on additional</i> A) Patient ~~did not date~~ <i>an additional</i> consent form for the <i>rel-gae</i> liver biopsy. <del></del> <i>samples obtained.</i>			
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<i>in addition</i> B) Patient [redacted] did not date ~~the~~ consent form for the <i>release</i> liver biopsy. ~~the~~ <i>samples</i> ~~the~~ <i>obtained</i> C) Patient [redacted] signed <i>an updated</i> consent form ~~the~~ <i>which was not properly identified as a follow-up consent form.</i> 10 - The informed consent process was not well documented in that it cannot always be determined who conducted the informed consent discussions and who answered questions from study patients. A) Patient [redacted] and witness signed the consent form for screening on 3/17/97, but the investigator signed it on 6/5/97. The study drug was administered on 6/13/97. B) The consent form for the liver biopsy for Patient [redacted] shows that the witness signature line was not signed or dated. C) Patient [redacted] signed the consent form for the liver biopsy on 5/20/98, but the witness signed it on 5/21/98. D) The consent forms (1) to act as a patient and (2) for the liver biopsy for patient [redacted] were not dated by the witness.			
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E) The consent form to act as a patient was signed by patient [REDACTED] on 9/20/98, but the witness signed it on 9/28/98. F) The consent form to act as a patient was signed by patient [REDACTED] on 10/29/98. The clinical investigator signed the form on 11/11/98, and the witness signed it on 11/6/98. G) The clinical research nurse signed and dated in the space designated for the investigator on the consent forms for (1) [REDACTED] testing and (2) for screening of Patient [REDACTED]. 11 - The sponsor/investigator did not submit a report of the death of two monkeys in study [REDACTED] entitled, "Evaluation of toxicity of [REDACTED] and [REDACTED] vectors in the liver of the non-human primate," to the FDA in a timely manner. This study was conducted from October 27, 1998, to December 10, 1998, concurrent with the OTCD study in human subjects. The report was submitted to FDA on October 27, 1999. 12 - Patients [REDACTED] and [REDACTED] developed grade III toxicities that were attributed to risk factors in the patients' medical histories. The sponsor/investigator did not incorporate these risk factors in the exclusion criteria of the protocol for the subsequent patients [REDACTED]. 13 - The protocol required that if a single patient developed grade III or higher toxicity, the study would be halted, and FDA and the IRB would be notified. The study would only resume after the FDA and the IRB granted permission.			
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A) Patient [REDACTED] developed grade III toxicity, and the sponsor/investigator did not notify the FDA prior to enrolling patient [REDACTED]. Patient [REDACTED] also developed grade III toxicity, and the sponsor/investigator did not stop the study, but proceeded to enroll patient [REDACTED] without FDA permission. B) - The sponsor/investigator did not notify the IRB of the grade III toxicities experienced by patients [REDACTED] and [REDACTED] as each adverse event occurred. The sponsor/investigator continued enrolling patients without permission of the IRB. 14 - Protocol's required laboratory test results were not available for review during the inspection for the following patients: <table border="1"> <thead> <tr> <th>Patient #</th> <th>Laboratory test(s)</th> <th>day(s) #</th> </tr> </thead> <tbody> <tr> <td>[REDACTED]</td> <td>differentials</td> <td>[REDACTED]</td> </tr> <tr> <td>[REDACTED]</td> <td>differentials</td> <td>[REDACTED]</td> </tr> <tr> <td>[REDACTED]</td> <td>differentials</td> <td>[REDACTED]</td> </tr> <tr> <td>[REDACTED]</td> <td>CBC</td> <td>[REDACTED]</td> </tr> <tr> <td>[REDACTED]</td> <td>differentials</td> <td>[REDACTED]</td> </tr> <tr> <td>[REDACTED]</td> <td>CBC/differentials</td> <td>[REDACTED]</td> </tr> </tbody> </table>				Patient #	Laboratory test(s)	day(s) #	[REDACTED]	differentials	[REDACTED]	[REDACTED]	differentials	[REDACTED]	[REDACTED]	differentials	[REDACTED]	[REDACTED]	CBC	[REDACTED]	[REDACTED]	differentials	[REDACTED]	[REDACTED]	CBC/differentials	[REDACTED]
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CBC differentials differentials differentials differentials differentials differentials differentials 15 - Protocol's required laboratory test results for [redacted] for day [redacted] were not available for review during the inspection for the following patients: # [redacted] and [redacted] 16 - Patient [redacted] was not followed to monitor the resolution of adverse events. This patient was discharged with a grade III [redacted] and was never retested to determine if or when the value returned to normal. 17 - The sponsor/investigator does not have documentation for training of the study staff.			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Mike M. Rasanti</i> <i>Thomas L. Eggerman</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Mike M. Rasanti/CSO Thomas L. Eggerman	DATE ISSUED 1/9/2000

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NAME OF INDIVIDUAL TO WHOM REPORT ISSUED To: James M. Wilson, M.D.		PERIOD OF INSPECTION See page 7	C. F. NUMBER 2531758
TITLE OF INDIVIDUAL Director Institute for Human Gene Therapy		TYPE ESTABLISHMENT INSPECTED Sponsor/Investigator	
FIRM NAME University of Pennsylvania Health System		NAME OF FIRM, BRANCH OR UNIT INSPECTED James M. Wilson, M.D.	
STREET ADDRESS 204 Wistar Institute, 3601 Spruce Street		STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Philadelphia, PA 19104-4268		CITY AND STATE (Zip Code) Same	
DURING AN INSPECTION OF YOUR FIRM, (WE) OBSERVED:			
18 - Inventories of the study drug could not be accounted for study drug lots # [REDACTED] and [REDACTED] which were used for patients # [REDACTED] Period of Inspection: 11/30; 12/1, 7-10, 13, 14, 16, 17, 20-22/1999; 1/7, 13, 19/2000			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Mike M. Rashti Thomas L. Eggerman	EMPLOYEE(S) NAME AND TITLE (Print or Type) MIKE M. RASHTI/CSO Thomas L. Eggerman/MO	DATE ISSUED 1/19/2000

FORM FDA 483 (5/85)

PREVIOUS EDITION MAY BE USED.

INSPECTIONAL OBSERVATIONS PAGE 7 OF 7 PAGES

[draft 1/19/00 11p, LB; 1/20/00 PDN; 1/21/00 pdn]

**Questions and Answers on Clinical Hold and FDA's Inspection
U. Penn. Gene Therapy Trial
January 21, 1999**

FOR INTERNAL USE ONLY

Q: What did FDA announce today?

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When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

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Q: Does this document reveal major new findings that were not disclosed in December?

A: It's important to understand that all the information disclosed last month was submitted by Dr. Wilson's group as part of his IND. The problems discussed then concerned deviations from the criteria for including patients, violations of the rules for stopping the trials, failure to report adverse reactions, and failure to report animal data promptly.

FDA inspected Dr. Wilson's operations to clarify the information submitted by Dr. Wilson. The inspection confirmed the problems already identified, and in addition found irregularities in the process for obtaining informed consent from research subjects and in signing the informed consent forms.

[Background: in addition, the sponsor lacked standard operating procedures, which are like a check list for keeping track of all the important tasks required in the protocol. It's an essential tool for documenting the progress of patients, any problems that occur, and adverse events. The SOP also helps the investigator make sure that accurate and timely information is transmitted to the agency concerning adverse events and changes in the protocol.]

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A: The data from the IND, as well as the results of FDA's inspection, raise concerns about the way this clinical trial was being conducted.

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A: Like all FDA inspections, inspections of clinical investigators are designed to determine whether regulations to protect patients and consumers are being followed.

At the end of an inspection, FDA typically discusses its findings with the sponsor or manufacturer. These discussions focus on how to bring the sponsor into compliance with regulations. It is FDA's expectation that the sponsor will work to remedy the deficiencies it found.

In issuing the Form 483, FDA is concluding this part of the investigation. But this case remains an open issue. Dr. Wilson has an opportunity to respond to those observations. FDA is continuing to examine all aspects of this case and is weighing next steps.

Q: Is FDA going to take any additional regulatory action on the basis of this inspection?

A: FDA does not discuss the possible outcome of open investigations. This report of FDA's inspection is but one step of the overall process. FDA will continue to weigh the information it has gathered and will take further action, if further action is warranted.

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Q: What effect does today's action have on other medical research at the University of Pennsylvania? On other gene therapy research?

A: FDA has an ongoing interest in evaluating measures to improve the conduct of clinical studies. Based on what we have learned from recent events, the following actions are being taken by the agency:

FDA is taking steps to improve patient safety by heightening its efforts to improve investigator compliance through:

-increasing its oversight of gene therapy INDs through increased inspections.

CBER is assessing which sponsors may need to obtain independent monitoring of their gene therapy INDs to improve conduct of clinical trials and to help ensure timely and accurate reporting to the FDA

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[Code of Federal Regulations]

[Title 21, Volume 5, Parts 300 to 499]

[Revised as of April 1, 1999]

From the U.S. Government Printing Office via GPO Access

[CITE: 21CFR312.42]

[Page 76-78]

TITLE 21--FOOD AND DRUGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES--Continued

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[[Page 77]]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Chief of Staff

Washington, D.C. 20201

FACSIMILE

DATE: 1/22TO: Devorah

FAX#: _____

*FDA
gene therapy
trials*

FROM: Liz Summy
Deputy Chief of Staff

D: A

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

*These came in late Friday
Sorry I didn't send them
then*

Liz

____ Pages [including this cover]

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[[Page 77]]

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C. K. Kellum

Melissa

From [signature]

[signature]

NIH and FDA Oversight of Gene Transfer Research Next Steps

NIH

The NIH process of public RAC review of safety, scientific, and ethical issues in gene transfer research has served the public, patients, and scientific community by promoting the safe and ethical conduct of this line of clinical research. A key component of this process is the provision of safety and toxicity data to the RAC by investigators and sponsors conducting gene transfer research. As set forth in the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*, NIH has in place a process for receiving serious adverse events reports and providing the data to the RAC for further evaluation and, if warranted, public discussion. The *NIH Guidelines* currently require the immediate reporting of all serious adverse events associated with human gene transfer clinical research. The *NIH Guidelines* apply to all NIH-funded projects involving recombinant DNA techniques as well as to all non-NIH funded research involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH funds for projects involving recombinant DNA.

In recent months, several developments have called into question the extent to which serious adverse event reports have been provided to the NIH and the RAC. In early September, the NIH raised concerns to the RAC regarding an emerging practice by gene transfer sponsors and investigators of labeling serious adverse events as confidential. This practice precludes public review of the events by the RAC and broader dissemination of the information to the scientific community. In response to subsequent events (the death of a patient enrolled in a gene transfer study at the University of Pennsylvania and additional safety and toxicity data collected by NIH in response), NIH is taking a number of steps, some in coordination with FDA and OPRR, to ensure that its role in oversight of gene transfer research is appropriate.

Fall 1999

NIH Calls for Safety Data on Adenoviral Vectors. In response to the death of the patient at the University of Pennsylvania, the NIH sent a letter on October 1, 1999 to all principal investigators using the same or similar method of gene delivery, requesting safety and toxicity data, including adverse events. A working group of the RAC was also formed to conduct an in-depth analysis of the data and, if necessary, develop guidance regarding the use of adenoviral vectors in gene transfer studies. In addition, plans were made to hold a scientific symposium at the upcoming December meeting of the RAC to provide comprehensive scientific review and public discussion of the data.

NIH/FDA Establish Adverse Event Notification Process. The NIH and FDA have established a new notification process for serious adverse events whereby FDA notifies the NIH when it receives serious adverse event reports from investigators and sponsors. One of the main goals of

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this information exchange is to enhance investigator compliance with the *NIH Guidelines*. The entire gene transfer research community was notified of the establishment of this process on November 5, 1999, in a letter from the FDA.

NIH Contacts All Institutions Conducting Gene Transfer Research. In a November 22 memorandum, NIH asked all institutions conducting human gene transfer research to review their institutional policies and procedures for ensuring compliance with the *NIH Guidelines*. This memorandum restates the requirements for serious adverse event reporting, directs institutions to ensure that they are in compliance with these reporting requirements, and requests that any institution not in compliance notify the NIH Office of Recombinant DNA Research within 15 days. A copy of the memorandum was sent to all Institutional Review Boards, Institutional Biosafety Committees, and Principal Investigators at institutions conducting human gene transfer studies.

NIH Proposes Amendments to Strengthen Compliance. The NIH proposed amendments to the *NIH Guidelines* that would emphasize and increase compliance with the current requirement to report all serious adverse events to NIH immediately. Our intent in proposing these changes is to ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided in a timely fashion to the RAC for review and analysis and, as necessary, public discussion. A proposed action to amend the *NIH Guidelines* was published in the November 22, 1999, *Federal Register* for public comment. The proposed action would add three provisions to the Guidelines: 1) a definition of serious adverse events and a stipulation of the time frame in which serious adverse events are to be reported in writing; 2) a mandate that serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential and that all information submitted in accordance with the Guidelines will be considered public unless NIH determines that there are exceptional circumstances; and 3) a directive that serious adverse event reports submitted to NIH be stripped of individually-identifiable patient information in order to ensure patient confidentiality. These changes will not only clarify the NIH requirements for reporting adverse events, but will ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided in a timely fashion to the RAC for review and analysis.

RAC Holds Symposium and Meeting December 8-10, 1999.

RAC Decides to Further Review Proposed Action. The RAC discussed the usefulness of submitting *all* serious adverse event reports to the NIH and the NIH resources that might be required to ensure the appropriate review and public discussion. There was no resolution of this complex issue; more discussion is needed and the working group will have to meet again. The discussion did, however, lean toward more reporting to the NIH -- not less. This position was reflected in much of the public comment. Industry representatives from the Biotechnology Industry Organization (BIO) and Schering-Plough articulated concerns about adverse event reporting to the NIH, the confidentiality of this information, and the burden and consequences of reporting. These concerns will be considered by the RAC Working Group in any recommended changes to the NIH Guidelines. What remains in question is the volume of information, the time frame in

which that information would be reported to the NIH, and how to harmonize the NIH and FDA requirements, so as not to unfairly burden the investigator.

RAC Receives Preliminary Recommendations of Working Group on Adenoviral Vectors in Gene Transfer Research. The Working Group's preliminary recommendations relate to the need for standardization of adenoviral vector production and quality control as well as to the need for additional patient selection criteria and monitoring procedures.

Winter 2000

NIH/FDA Initiate Comparative Analysis. The NIH and FDA are initiating a comparative analysis of the number of serious adverse events in human gene therapy trials reported to each agency. This analysis will provide important information regarding investigator compliance with Federal requirements for serious adverse event reporting.

NIH Establishes Advisory Committee to the Director (ACD) Working Group to Review NIH Oversight Role. As part of NIH's response to recent events, the NIH Director established a working group of the ACD to review the role of the NIH in oversight of clinical gene transfer research. The Working Group is being encouraged to consult with other experts and solicit public comment in the course of its work. The Working Group is asked to develop recommendations to address the following questions: 1) Is the current NIH framework for oversight and public discussion of clinical gene transfer research appropriate, especially with regard to the respective roles of the RAC and the NIH Guidelines; 2) Are current NIH mechanisms adequate for coordination of the oversight of clinical gene transfer research with FDA, OPRR, IRBs, and IBCs; 3) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research; and 4) What should the NIH role be with regard to reporting, analysis and public discussion of serious adverse events?



RAC to Make Recommendations to NIH Director on Serious Adverse Event Reporting. In light of public comment received, RAC discussion, and subsequent consideration by the RAC Working Group, the RAC will consider a revised proposal for amending the *NIH Guidelines* on serious adverse event reporting and transmit final recommendations to the NIH Director for consideration.

RAC to Make Recommendations to NIH Director on Use of Adenoviral Vectors in Gene Transfer Clinical Research. The RAC will develop a final report of its conclusions and recommendations on the use of adenoviral vectors in human gene transfer research. If the RAC determines that further guidance is needed about the use of adenoviral vectors, a proposal will be issued for public comment. After consideration of the public comment, RAC will transmit final recommendations to the NIH Director. If approved by the Director, this guidance will be incorporated into the *NIH Guidelines*.

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Fall-Winter 2000

 **NIH Human Gene Transfer Information System (HGTIS) Scheduled to be On-line.** The HGTIS is a computerized database containing current information about all gene transfer clinical trials in the U.S. The information contained in the database will describe the key components of each protocol as well as safety and efficacy data. The ultimate goal of the database is to enhance awareness of new developments in gene transfer research and to disseminate important safety information to the general public, patients, and the scientific community. Phase I of the database is expected to be completed toward the end of 2000.

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FDA/CBER 12-13-99

FDA

Human gene therapy products represent one of the fastest growing areas of product development under FDA oversight. In addition to challenging traditional FDA regulatory policies and regulations, gene therapy products and their uses present extraordinary novel and controversial issues associated with cutting edge medical technology, ranging from the use of mouse and human viruses to produce gene vectors, to the ethical and social issues involved with potential in utero attempts for gene alteration. From 1989 to the present, over 280 new gene therapy INDs were submitted to FDA, with 55 submitted in FY 1999. As of November 23, 1999, 204 INDs are still active, with over 2,000 supplements to these INDs submitted each year.

Gene therapy protocols have an unusual distinction in that, in addition to FDA regulation, the Recombinant DNA Advisory Committee (RAC, which advises the NIH Director) provides public discussion of safety, ethical, and societal issues related to proposed and ongoing gene therapy protocols. FDA and NIH have consolidated their reviews of gene therapies and have held public prospective discussions with the RAC designated Gene Therapy Policy Conferences (GTPC) on major ethical issues such as in utero and germline gene therapy protocols. FDA has ex officio representation at each meeting of the RAC, and FDA members often bring complex issues for public discussion at the RAC. The Office of Biotechnology Activities (OBA) at NIH will be responsible for annual data reporting, which includes patient accrual, adverse events, and scientific and medical reports, and for administering the RAC.

Fall 1999

September 1999- FDA notified of death of patient in a gene therapy trial for ornithine transcarbamylase (OTC) deficiency. FDA placed the trial on clinical hold and informed the sponsor that presentation at the next meeting of the RAC would likely be required. FDA reviewers identify other gene therapy protocols using adenoviral vectors intravascularly and contacted sponsors to alert them of the death, and to add appropriate language to the informed consent.

October 1999 - Two protocols by Schering Corporation using intrahepatic inoculation of high dose adenoviral vector for cancer put on clinical hold, due to similarity of route of administration and dose. Receipt of additional materials provided by OTC sponsor showed that pertinent animal data had not been submitted to the Agency before. FDA also established several protocol violations involving two patients with grade III liver enzyme toxicities, and questions on the ammonia levels before treatment in the patient who eventually died.

November 1999 - FDA issues letters to gene therapy sponsors reminding them of their additional requirements under the NIH Recombinant DNA Guidelines, including timing of submission of

FDA/CBER 12-13-99

protocols to the Office of Biotechnology Activities before submission as an IND to FDA, and a reminder of the requirements for timely reporting to OBA/RAC of adverse events and changes to protocols.

* December 7, 1999 - FDA implements two new Standard Operating Procedures that, on a weekly basis, notifies OBA of FDA receipt of adverse events in gene therapy protocols and changes in gene therapy protocols.

December 7-10 - FDA reviewers participates as ad hoc members on the Working Group on Adenoviral Vectors, and presents information related to the OTC protocol, and FDA regulations on adverse event reporting at the RAC Symposium and Meeting December 8-10.meeting.

Winter 2000

* FDA will publish a proposed rule that will greatly increase public disclosure of information contained in gene therapy INDS and xenotransplantation INDS. This will include both expedited (15 day) and annual reports of adverse events; continuous reporting of changes to protocols through the life of the IND and Biologics License Application, and will have mechanisms for transmission of disclosable information from FDA to OBA to reduce duplication of submissions.

Ongoing FDA-NIH Interactions

FDA has worked closely with NIH and the RAC regarding gene transfer clinical research since 1992. FDA and NIH co-sponsored Gene Therapy Workshops in 1996 and 1997 with over 800 attendees at both conferences. By combining a large regulatory educational session with an extended scientific session, FDA has educated the sponsors in this field to submit more complete INDS, which has greatly enhanced FDA reviewer productivity. FDA has continued these efforts with educational symposia at the 1998 and 1999 annual meetings of the American Society for Gene Therapy.

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number of gene therapy INDs put on clinical hold because of preclinical findings of persistent vector signal in gonadal tissues. The results of the discussions have led to new FDA policies on reproductive risks for gene therapy that have been presented at the RAC in June of 1999, and discussed in Nature Genetics in August of 1999.

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this information exchange is to enhance investigator compliance with the *NIH Guidelines*. The entire gene transfer research community was notified of the establishment of this process on November 5, 1999, in a letter from the FDA.

NIH Contacts All Institutions Conducting Gene Transfer Research. In a November 22 memorandum, NIH asked all institutions conducting human gene transfer research to review their institutional policies and procedures for ensuring compliance with the *NIH Guidelines*. This memorandum restates the requirements for serious adverse event reporting, directs institutions to ensure that they are in compliance with these reporting requirements, and requests that any institution not in compliance notify the NIH Office of Recombinant DNA Research within 15 days. A copy of the memorandum was sent to all Institutional Review Boards, Institutional Biosafety Committees, and Principal Investigators at institutions conducting human gene transfer studies.

NIH Proposes Amendments to Strengthen Compliance. The NIH proposed amendments to the *NIH Guidelines* that would emphasize and increase compliance with the current requirement to report all serious adverse events to NIH immediately. Our intent in proposing these changes is to ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided in a timely fashion to the RAC for review and analysis and, as necessary, public discussion. A proposed action to amend the *NIH Guidelines* was published in the November 22, 1999, *Federal Register* for public comment. The proposed action would add three provisions to the Guidelines: 1) a definition of serious adverse events and a stipulation of the time frame in which serious adverse events are to be reported in writing; 2) a mandate that serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential and that all information submitted in accordance with the Guidelines will be considered public unless NIH determines that there are exceptional circumstances; and 3) a directive that serious adverse event reports submitted to NIH be stripped of individually-identifiable patient information in order to ensure patient confidentiality. These changes will not only clarify the NIH requirements for reporting adverse events, but will ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided in a timely fashion to the RAC for review and analysis.

RAC Holds Symposium and Meeting December 8-10, 1999.

RAC Decides to Further Review Proposed Action. The RAC discussed the usefulness of submitting *all* serious adverse event reports to the NIH and the NIH resources that might be required to ensure the appropriate review and public discussion. There was no resolution of this complex issue; more discussion is needed and the working group will have to meet again. The discussion did, however, lean toward more reporting to the NIH -- not less. This position was reflected in much of the public comment. Industry representatives from the Biotechnology Industry Organization (BIO) and Schering-Plough articulated concerns about adverse event reporting to the NIH, the confidentiality of this information, and the burden and consequences of reporting. These concerns will be considered by the RAC Working Group in any recommended changes to the NIH Guidelines. What remains in question is the volume of information, the time frame in

which that information would be reported to the NIH, and how to harmonize the NIH and FDA requirements, so as not to unfairly burden the investigator.

RAC Receives Preliminary Recommendations of Working Group on Adenoviral Vectors in Gene Transfer Research. The Working Group's preliminary recommendations relate to the need for standardization of adenoviral vector production and quality control as well as to the need for additional patient selection criteria and monitoring procedures.

Winter 2000

NIH/FDA Initiate Comparative Analysis. The NIH and FDA are initiating a comparative analysis of the number of serious adverse events in human gene therapy trials reported to each agency. This analysis will provide important information regarding investigator compliance with Federal requirements for serious adverse event reporting.

NIH Establishes Advisory Committee to the Director (ACD) Working Group to Review NIH Oversight Role. As part of NIH's response to recent events, the NIH Director established a working group of the ACD to review the role of the NIH in oversight of clinical gene transfer research. The Working Group is being encouraged to consult with other experts and solicit public comment in the course of its work. The Working Group is asked to develop recommendations to address the following questions: 1) Is the current NIH framework for oversight and public discussion of clinical gene transfer research appropriate, especially with regard to the respective roles of the RAC and the NIH Guidelines; 2) Are current NIH mechanisms adequate for coordination of the oversight of clinical gene transfer research with FDA, OPRR, IRBs, and IBCs; 3) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research; and 4) What should the NIH role be with regard to reporting, analysis and public discussion of serious adverse events?

RAC to Make Recommendations to NIH Director on Serious Adverse Event Reporting. In light of public comment received, RAC discussion, and subsequent consideration by the RAC Working Group, the RAC will consider a revised proposal for amending the *NIH Guidelines* on serious adverse event reporting and transmit final recommendations to the NIH Director for consideration.

RAC to Make Recommendations to NIH Director on Use of Adenoviral Vectors in Gene Transfer Clinical Research. The RAC will develop a final report of its conclusions and recommendations on the use of adenoviral vectors in human gene transfer research. If the RAC determines that further guidance is needed about the use of adenoviral vectors, a proposal will be issued for public comment. After consideration of the public comment, RAC will transmit final recommendations to the NIH Director. If approved by the Director, this guidance will be incorporated into the *NIH Guidelines*.

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Fall-Winter 2000

NIH Human Gene Transfer Information System (HGTIS) Scheduled to be On-line. The HGTIS is a computerized database containing current information about all gene transfer clinical trials in the U.S. The information contained in the database will describe the key components of each protocol as well as safety and efficacy data. The ultimate goal of the database is to enhance awareness of new developments in gene transfer research and to disseminate important safety information to the general public, patients, and the scientific community. Phase I of the database is expected to be completed toward the end of 2000.

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FDA

Human gene therapy products represent one of the fastest growing areas of product development under FDA oversight. In addition to challenging traditional FDA regulatory policies and regulations, gene therapy products and their uses present extraordinary novel and controversial issues associated with cutting edge medical technology, ranging from the use of mouse and human viruses to produce gene vectors, to the ethical and social issues involved with potential in utero attempts for gene alteration. From 1989 to the present, over 280 new gene therapy INDs were submitted to FDA, with 55 submitted in FY 1999. As of November 23, 1999, 204 INDs are still active, with over 2,000 supplements to these INDs submitted each year.

Gene therapy protocols have an unusual distinction in that, in addition to FDA regulation, the Recombinant DNA Advisory Committee (RAC, which advises the NIH Director) provides public discussion of safety, ethical, and societal issues related to proposed and ongoing gene therapy protocols. FDA and NIH have consolidated their reviews of gene therapies and have held public prospective discussions with the RAC designated Gene Therapy Policy Conferences (GTPC) on major ethical issues such as in utero and germline gene therapy protocols. FDA has ex officio representation at each meeting of the RAC, and FDA members often bring complex issues for public discussion at the RAC. The Office of Biotechnology Activities (OBA) at NIH will be responsible for annual data reporting, which includes patient accrual, adverse events, and scientific and medical reports, and for administering the RAC.

Fall 1999

September 1999- FDA notified of death of patient in a gene therapy trial for ornithine transcarbamylase (OTC) deficiency. FDA placed the trial on clinical hold and informed the sponsor that presentation at the next meeting of the RAC would likely be required. FDA reviewers identify other gene therapy protocols using adenoviral vectors intravascularly and contacted sponsors to alert them of the death, and to add appropriate language to the informed consent.

October 1999 - Two protocols by Schering Corporation using intrahepatic inoculation of high dose adenoviral vector for cancer put on clinical hold, due to similarity of route of administration and dose. Receipt of additional materials provided by OTC sponsor showed that pertinent animal data had not been submitted to the Agency before. FDA also established several protocol violations involving two patients with grade III liver enzyme toxicities, and questions on the ammonia levels before treatment in the patient who eventually died.

November 1999 - FDA issues letters to gene therapy sponsors reminding them of their additional requirements under the NIH Recombinant DNA Guidelines, including timing of submission of

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protocols to the Office of Biotechnology Activities before submission as an IND to FDA, and a reminder of the requirements for timely reporting to OBA/RAC of adverse events and changes to protocols.

December 7, 1999 - FDA implements two new Standard Operating Procedures that, on a weekly basis, notifies OBA of FDA receipt of adverse events in gene therapy protocols and changes in gene therapy protocols.

December 7-10 - FDA reviewers participates as ad hoc members on the Working Group on Adenoviral Vectors, and presents information related to the OTC protocol, and FDA regulations on adverse event reporting at the RAC Symposium and Meeting December 8-10.meeting.

Winter 2000

FDA will publish a proposed rule that will greatly increase public disclosure of information contained in gene therapy INDS and xenotransplantation INDS. This will include both expedited (15 day) and annual reports of adverse events; continuous reporting of changes to protocols through the life of the IND and Biologics License Application, and will have mechanisms for transmission of disclosable information from FDA to OBA to reduce duplication of submissions.

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