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UNITED STATES ATTORNEY'S OFFICE
NEWS RELEASE

U.S. SETTLES CASE OF GENE THERAPY STUDY THAT ENDED WITH TEEN'S DEATH

February 9, 2005 - PHILADELPHIA – United States Attorney Patrick L. Meehan today announced that the government has reached civil settlements stemming from a University of Pennsylvania gene therapy study that ended with the death of a participant; Arizona teenager Jesse Gelsinger. The settlements cover alleged false statements and claims made between July 1998 through September 1999.

This is a model enforcement action because it includes both individual researchers as well as research institutions in a civil fraud matter. In this case, the University of Pennsylvania (Penn) has agreed to pay $517,496 and Children's National Medical Center (CNMC) has agreed to pay $514,622 to the government to resolve the government's allegations. In addition, the three named investigators, Drs. James Wilson, Mark Batshaw, and Steven Raper, will have restrictive controls on their clinical research activities as set forth in the settlement agreements. The restrictions applicable to Dr. Wilson are more severe given his pivotal role as sponsor in the clinical trial in which Jesse Gelsinger participated.

"Perhaps most significant is the impact that these settlements will have on the way clinical research on human participants is conducted throughout the country," said Meehan. "This action covers two major research centers which have instituted important changes in the conduct and monitoring of clinical research on human participants. We hope that these settlements will now serve as a model for similar research nationwide."

The settlement arises out of human research participants' involvement in the development of an investigational new drug to treat a certain deficiency in an enzyme called ornithine transcarbamylase (OTC). The urea cycle, located in the liver, detoxifies nitrogen and changes it to urea which is nontoxic and can then be excreted as urine. Some individuals are unable to convert nitrogen (ammonia) to urea because they are born with deficient or absent activity of OTC, an essential enzyme for making urea. A high level of ammonia is toxic to the central nervous system, and as a result hyperammonaemic coma and death may occur with OTC deficiency (OTCD).

The Phase I safety study focused on the use of a genetically engineered adenovirus being inserted into human subjects to address OTCD. The OTC gene was placed inside a virus called adenovirus, and the virus was injected into the liver through blood vessels. The virus then carried the OTC gene into the research participant's liver cells and once in the liver cells, the OTC gene was to produce the OTC enzyme that is missing in OTCD.

INVESTIGATION:

The government has alleged, among other allegations, that the study had produced toxicities in humans that should have resulted in termination, but the study continued. Reports were submitted to FDA, NIH and to the Institutional Review Boards (IRBs) charged with oversight of this study that misrepresented the actual clinical findings associated with the study. Additionally, the consent form and process did not disclose all anticipated toxicities.

The government allegations contained in the settlements with Penn, CNMC, Wilson, Batshaw and Raper address several violations of the civil False Claims Act that occurred between July 1998 through September 1999. We contend that the individuals and their institutions (as the recipients of federal funding) submitted and/or caused to be submitted: (1) false statements and claims in connection with the submission of grant applications, progress reports, and annual reports to, and receipt of federal funds from, the NIH; (2) false statements and claims in connection with submissions to the FDA; (3) false statements and claims in connection with the failure to obtain properly informed consent from human research participants; and (4) false statements made to IRBs charged with oversight of this research.

As set forth in the Agreements, Penn, CNMC, and Drs. Wilson, Batshaw and Raper do not admit to the government's allegations and contend that their conduct was at all times lawful and appropriate.

SETTLEMENTS:

The terms of the agreement for Dr. Wilson are as follows:

1. Dr. Wilson will not serve as a sponsor of an FDA-regulated clinical trial for a five-year period starting today. He has not been involved with human research participants since January 2000.

2. Dr. Wilson must meet imposed training/educational requirements applicable to human research participant protections and clinical research.

3. Dr. Wilson must conduct restricted clinical activity with a Medical Monitor (approved by the government and paid for by sponsor or grantee) and/or a Contract Research Organization (paid for by sponsor or grantee) for a period of 3 years to gain practical experience. Dr. Wilson may only conduct restricted clinical activity in one study at a time only after he completes the educational requirement.

4. A Special Monitor (SM) will be utilized to oversee Dr. Wilson's research when, as part of a larger clinical research grant, his animal research could influence the safety of human research participants. The SM will oversee Dr. Wilson's activities to: a) ascertain whether his involvement constitutes Restricted Clinical Activity, b) ensure information related to the safety of humans is communicated to the IRB, sponsor and grantee, and c) ascertain Dr. Wilson's compliance with regulatory requirements. The SM will be required to submit semi-annual reports to NIH and FDA.

5. If Dr. Wilson submits a grant application to the NIH that involves human participants, he must notify the Office of Policy for Extramural Research Administration (OPERA). OPERA will ensure that the NIH Institute and/or Center extramural staff is informed regarding the special terms and conditions that will be imposed throughout the 5-year period.

6. Dr. Wilson will not be eligible to participate without restriction in human participants' research for 5 years from the date of the agreement, i.e., February 9, 2005. If Dr. Wilson does not complete the training and three year supervised research requirements, he will remain restricted.

7. Dr. Wilson has agreed to lecture and author an article on the lessons learned from this study. Dr. Wilson has agreed to advocate for the inclusion of any statements from those affected by the study, e.g., the Gelsinger family. This statement will be at the discretion of the Gelsingers.

For **3 years**, commencing on dates as set forth in their respective Agreements, the following restrictions will be imposed on Drs. Batshaw and Raper:

1. Educational and training requirements applicable to human research participant protections and clinical research must be completed.

2. Conduct restricted clinical activities with a Clinical Research Organization (CRO) and/or Research Administrator (RA) to oversee compliance with applicable regulations. Semi-annual reports will be provided to the federal government by the CRO and/or RA when conducting human subjects research activities.

3. Conduct restricted clinical activities with a Medical Monitor (M/M) to review performance of human clinical research projects to ensure the protection of human research participants in clinical activities. Semi-annual reports will be provided to NIH and FDA by the M/M to ensure compliance throughout the 3-year period.

The Institutions are settling the monetary component to the government's allegations
and have implemented meaningful corrective action plans to address the protection of human research participants. These systemic changes include:

University of Pennsylvania

• Increased Institutional Review Board (IRB) oversight of clinical research and a comprehensive program to ensure research participant safety

• Mandatory training for all investigators and clinical coordinators who participate in clinical research—training topics include regulatory requirements, conflict of interest, Good Clinical Practices, Informed Consent, Adverse Events, Data and Safety Monitoring

• Policy that ensures that an IRB will not review a protocol without submission of certification that training was completed

• Strengthened Standard Operating Procedures (SOPs) to provide a clearer delineation of roles and responsibilities of sponsors and investigators

• Initial monitoring and oversight of clinical research through an independent Contract Research Organization (CRO) and the creation of the Office of Human Research (OHR) under the Vice Dean for Research and Research Training. OHR's mission is to promote human research while ensuring the highest level of research participant safety.

• Established internal monitoring function of high risk studies. OHR reviews informed consent, adverse event reporting and compliance with protocols

Children's National Medical Center

• IRB staff has been increased—2 to 5 including Administrative Director

• Financial commitment to compliance by a 50% increase in the IRB budget between 2001-2004

• The addition of an RN Quality Improvement Coordinator hired in 2003

• New Research Subject Advocate—bilingual pediatrician/medical ethicist to review all Pediatric Clinical Research Center protocols and consent forms prior to IRB submission and to:

Assist investigators in formulating and reviewing data and safety monitoring plans

Observe research consent process periodically (at least once per protocol) and provide feedback to the Principal Investigator

Obtain feedback from families and research participants regarding recruitment and informed consent process and provide it to the Principal Investigator

Monitor adverse event reporting

Government's Regulatory Response Regarding Gene Therapy

"Today's settlements restricting the research of key investigators in a gene therapy trial illustrates FDA's commitment to enforce regulations designed to protect research subjects," said Acting FDA Commissioner Dr. Lester M. Crawford. "Although gene therapy has tremendous potential to benefit patients, the tragic death of Jesse Gelsinger reminds us that sponsors who conduct clinical trials must take seriously their responsibility to make these trials as safe as possible."

In an effort in provide greater protection for people participating in clinical research, FDA's Center for Biologics Evaluation and Research (CBER) took steps following the revelations in the

gene therapy study to enhance the surveillance of clinical research by increasing inspections of gene therapy clinical investigators. Inspections of ongoing studies have been expanded to cover clinical studies for all biological products regulated by CBER.

The case was investigated by the FDA's Office of Criminal Investigations and the HHS-Office of Inspector General. In addition, representatives from the NIH and FDA were instrumental in resolving this matter. The case was handled by Assistant United States Attorney David R. Hoffman.

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***An Indictment or Information is an accusation. A defendant is presumed innocent unless and until proven guilty.**

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