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Domestic Policy Council

Box 5 of 7

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Enclosures filed in
Oversize Attachments # 20472
NARA #17675

Brochures welcoming the President to the Washington Home and Hospice of Washington

Cards offer health care savings

But may promise more than they can deliver, critics say

By Julie Appleby
USA TODAY

No health insurance? No problem, say dozens of companies hawking medical discount cards as a controversial answer to the rising cost of health care and the growing number of uninsured.

Pay monthly fees ranging from \$6.50 to about \$40, and the cards promise savings of up to 80% on doctor visits, prescriptions, eyeglasses or dental care. One card even throws in cut-rate veterinary services.

Critics, however, urge caution, saying the cards can promise more than they deliver.

"There's no guarantee that the people paying premiums will get the benefits they are paying for," says Julie Stewart, spokeswoman for the California Department of Corporations, which recently warned 46 card sellers to stop doing business in the state.

The cards are sold over the Internet and by commission-earning agents, who often aim their pitches at the uninsured and the elderly. Promoters say the cards give buyers discounts equal to the rates negotiated by large insurers.

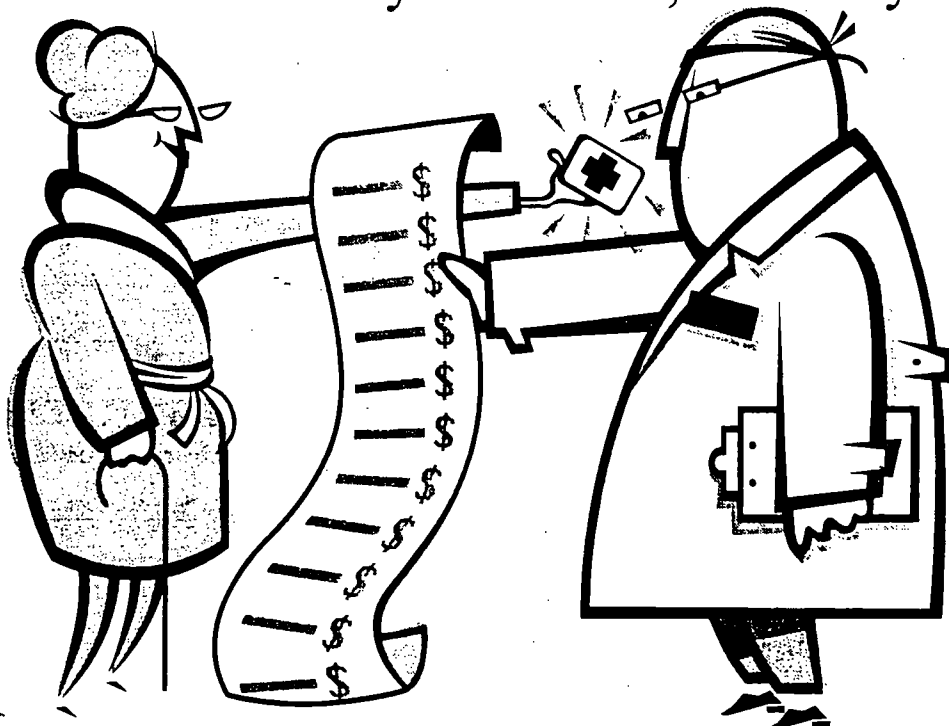
"We'd seen some of the discount rates negotiated by insurers for physician and hospital care and I thought, why couldn't we negotiate the same thing for patients?" says John Luther, vice president of sales for Care Entrée, a Dallas-based savings card.

Patient Pat Hollan of Smithville, Texas, says she saved more than \$8,000 by using the \$40-a-month Care Entrée card when her husband needed surgery for a kidney stone.

She uses the card instead of buying insurance, saying a good policy would cost her about \$500 a month. Hollan figures she's saving money even if she occasionally has to shell out a few thousand dollars on a hospital bill.

"I just love it," Hollan says. "I get real good discounts."

But consumer groups are wary, saying the cards should not be a substitute for comprehensive health insurance. Nor do they think such cards will help most of the uninsured, because many could not afford even the discounted fees, especially if



By Alejandro Gonzalez, USA TODAY

hospital care is required.

Additional oversight

Some states want additional oversight. In addition to California, regulators in Washington and Arkansas have cracked down on card sellers. Although card sellers go to lengths to say the plans are not insurance, regulators say they must meet financial solvency and other criteria required of insurers.

"We get complaints all the time," says Jim Stevenson, spokesman for Washington's insurance commissioner.

Problems include providers who don't stick to the purported discount rates or add on charges. Savings from the cards may be no greater than what can be had without paying monthly fees, regulators say, and some cards may misrepresent the number of providers available in a given area.

In addition, some physicians may not be aware that their networks have contracted with these cards, despite being listed on the cards' Web sites as participating providers.

The cards vary in the types of services offered. Some are aimed at people who want discounts only on specific medical

services, such as vision or dental care, alternative medicine or chiropractors. Other cards offer discounts on a wide range of services, including networks of doctors and hospitals.

Variations of the savings cards are sold by such well-known companies as JC Penney, Sears and General Electric's Partnership Marketing Group, which offer discounts on dental care, optical services and drugs, but not medical doctors.

Other cards are sold by small companies with only an Internet address.

How they work

After paying the monthly fee, buyers are sent a list of providers who, the cards say, have agreed to offer discounts from 15% to 80% off "retail" or "usual and customary fees."

In exchange, the patient agrees to pay in full on the spot for the medical care provided.

Proponents say the cards help those without insurance. Doctors, they say, like the idea because they get paid right away. "We saw this as an opportunity to channel more business to providers," says James Herrington, chief marketing of-

ficer for Private Healthcare Systems, a network of about 300,000 doctors that contracts directly with at least two plans.

But Herrington objects to the sales pitches of some companies, which tout the card for the uninsured.

"This is absolutely not the answer to the uninsured," Herrington says. Instead, he says, the cards work best for patients with high-deductible medical plans, those with medical savings accounts and those looking to add benefits not covered by their health insurance, such as chiropractic care or dental services.

Buying from a well-known company, and considering the card a supplement for such items as eyeglasses or dental care not covered by regular insurance, might be beneficial for some consumers, says Judy Waxman of Families USA, an advocacy group.

Even so, Waxman and others urge buyers to check whether the services they want are covered and try to find out just how much they would save by buying the card.

"I think the message for consumers is to proceed with caution," says Gail Shearer of Consumers Union.

Gene-therapy patient died of the procedure, scientists determine

By Tim Friend
USA TODAY

A young man who died while undergoing a gene-therapy experiment was killed by the procedure, raising concerns that human experiments are moving ahead too aggressively.

Jesse Gelsinger's death was the first from a gene-therapy trial to be publicly reported.

Gelsinger, 18, of Tucson, died Sept. 17 from a virus used to deliver genes into his bloodstream during an experiment at the University of Pennsylvania, scientists concluded Wednesday.

"The (virus) did indeed initiate a sequence of events that led to the patient's death," says James Wilson, head of the research team treating Gelsinger.

The death has prompted added scrutiny of gene therapy, a rapidly evolving area of medical research in which healthy genes are delivered to the body to replace or restore genes that are absent or malfunctioning, causing disease.

Critics say the human experiments are moving forward too fast and without enough attention to problems that have shown up in animal studies.

The National Institutes of Health called for an extensive review of the circumstances surrounding the death

and asked other gene-therapy researchers involved in dozens of other studies to review their own data for potential problems.

The primary vehicles for delivering genes into the cells of the body are cold viruses that have had their disease-causing portions deleted but their cell-seizing machinery left intact.

Gelsinger was being treated for a rare metabolic disorder called ornithine transcarbamylase deficiency (OTC). Wilson says genes were delivered directly into the liver using a common cold virus, called an adenovirus.

Gelsinger first experienced an immune response and fever, followed by liver damage and extensive blood clotting. He appeared to improve, then underwent sudden respiratory distress, which killed him.

Immune reactions and blood clotting had been observed before in primate studies, but respiratory distress had not been seen before, Wilson says. Other patients received similar doses of the virus but had not experienced such severe reactions, he says.

Wilson says Gelsinger's blood marrow showed abnormalities that may have existed before the study. He does not know whether those abnormalities led to Gelsinger's reaction.

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USA TODAY · THURSDAY, DECEMBER 2, 1999

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White House Trims Its Energy Bills

Program Has Saved \$1.4 Million Since '93

By STEPHEN BARR
Washington Post Staff Writer

Energy-efficient measures and other steps taken as part of a "greening of the White House" initiative have saved taxpayers nearly \$1.4 million since 1993, according to an administration report scheduled for release today.

The savings, now running about \$300,000 a year at the White House, have been achieved through more efficient lighting, heating and air conditioning, new water sprinklers and other modifications. Lighting changes alone are saving about \$138,000 annually, officials said.

President Clinton announced the energy-saving project for the White House complex, including what is now known as the Eisenhower Executive Office Building, on Earth Day in 1993. "This has been his baby from the beginning," said Roger Ballantine, deputy assistant to the president for environmental initiatives.

Today's announcement, Ballantine said, shows "we've now done it" and that the White House is ready to move onto the next step—a new government-wide energy efficiency effort. In an executive order this summer, Clinton directed agencies to draw up conservation plans that would save \$750 million annually by 2010.

Energy Secretary Bill Richardson and Environmental Protection Agency Administrator Carol M. Browner are scheduled to release the "greening" report at the White House this morning. Officials said they will point out that many of the White House energy improvements came from commercially available, "off the shelf" materials and technology that most Americans can purchase for their homes and offices.

Clinton, of course, is not the first president to try to make the 200-year-old White House more environmentally friendly. President Jimmy Carter, in particular,

made it a habit to turn off White House lights and installed a solar panel (removed during the Reagan administration) on the West Wing roof.

But the Clinton project has been able to take advantage of new technology and techniques developed in recent years. Architects, Potomac Electric Power Co. experts and federal agency officials were called upon by the President's Council on Environmental Quality to devise a strategy for the White House complex, which covers about 19 acres.

At the White House, incandescent table lamp bulbs were replaced with compact fluorescent bulbs, with some exceptions made for antiques or for security purposes. Steps were taken to take better advantage of natural light and to ensure electric lights got turned off in rooms not in use. Exterior flood lights were replaced with more efficient halogen lights, which were hooked to timers to reduce energy waste.

The White House team also installed a new heating and air conditioning system in the executive residence this year, put new insulation on pipes and reduced steam loss. Even high-efficiency refrigerators were installed in the White House kitchen.

Next door at the Eisenhower Building, virtually all of the windows in the 1888 granite structure were replaced with double-paned glass, except when historical considerations took priority.

As offices replaced computers, printers and fax machines, they purchased energy-saving models that consume much less electricity.

On the White House grounds, the use of pesticides was sharply cut back and sprinklers were reset to operate in the early morning as part of a water conservation effort.

The White House also began participating in pilot programs to test alternative-fuel vehicles and an electric pickup truck.

Paul London
James Costello
USA

Scientists Decode Layout Of Human Chromosome

By RICK WEISS
Washington Post Staff Writer

A1

Scientists from three countries announced yesterday that they had jointly determined the piece-by-piece order of virtually all of the 34 million chemical "letters" that spell out the genetic code of an entire human chromosome.

The achievement provides the first complete molecular script for a single human chromosome, 23 pairs of which carry the estimated 80,000 genes that provide the instructions for constructing a human body.

Researchers around the world praised the advance as a technical tour de force, a triumph of international scientific collaboration, and evidence that the publicly funded Human Genome Project is on track to sequencing by 2002 all of the 3.2 billion units of genetic code that together describe how to make a person.

Scientists hope that by noting "spelling errors" in the chromosomes of people with various dis-

eases, they will be able to understand the molecular underpinnings of those ailments and develop new therapies. But first they must determine the normal sequences for each chromosome, as they now have for chromosome 22, the second smallest of the human chromosomes.

"For the hundreds of genes that are on this chromosome, we now have their anatomy," said Francis Collins, chief of the National Human Genome Research Institute, which funded most of the U.S. contribution to the project. "And for all the medical conditions [that are related to genes on that chromosome], we'll be that much further along understanding them."

About three dozen diseases are known to be caused by faulty genes on chromosome 22. Most are rare, such as DiGeorge syndrome, which involves abnormal skull development, and there is indirect evidence that a gene on chromosome 22 may contribute to the risk of schizophrenia. But with scientists expecting to find a total of 700 or 800 genes embedded in the chromosome's code, scores of other diseases may eventually be shown to have their roots there.

"I can tell you it is no fun chasing down a disease gene when you're in territory no one has ever been in before," Collins said at a Washington news conference yesterday. For scientists hunting for important genes on chromosome 22, he said, having the complete sequence in hand is "a dream come true."

Chromosomal sequence analysis also may provide insights into human evolution, because large chunks of molecular text in human chromosomes are very similar to certain DNA chunks in animal chromosomes. A comparison of those molecular scripts could reveal how and when various organisms branched off from one another and diverged over millions of years.

"It's like seeing the surface or the landscape of a new planet for the first time," said Mark Patterson, an editor at *Nature*, the scientific journal that is publishing the chromo-

somes report today. "It's allowing us to say something about its geography, and it's also allowing us to say something about its history, ... how the chromosome evolved."

A chromosome, like a skein of yarn, is a single long strand of DNA folded and refolded into a plump, cinch-waisted bundle inside a cell. The DNA strand is made of four chemical subunits—the four "letters" of the genetic alphabet—strung together by the millions. Anywhere from 1,000 to a half-million of those letters typically make up a gene, and the order of the

letters within the gene determines what the gene does in the body.

The exact meaning of chromosome 22's molecular sequence remains mostly a mystery. In some ways, it's like a long run-on sentence in a foreign language for which only a modest number of words have been translated into English. Scientists understood what the translated words mean, and they now know the remaining letters, but most of it remains untranslated and therefore the meaning remains unknown. Moreover, only about 3 percent of the script is believed to encode working genes, with most of the rest of the sequence being "junk" DNA, the function of which remains unknown.

But with chromosome 22's complete script in hand—and with similar texts already being translated in other organisms, such as the mouse and the fruit fly—scientists said it won't be long before they become fluent in the language of human genes and begin to make profound discoveries about embryo development, genetic diseases and aging.

The scientific report lists more than 200 scientists as co-authors, an astonishing number that *Nature* editors said was probably a record. Four institutions cooperated in the venture: the Sanger Center in Cambridge, England; Keio University School of Medicine in Tokyo; the University of Oklahoma in Norman; and Washington University in St. Louis.

Technically, the sequence is not 100 percent complete. Small gaps, constituting a total of about 3 percent of the chromosome's "letters," have proven impossible to decode,

in some cases because they contain confusing strings of repeating motifs. And one specialized end of the chromosome, the DNA of which helps cells make another kind of genetic material called RNA, is not included in the new analysis.

But according to a 1996 international convention, a chromosome that is at least 95 percent sequenced and whose remaining gaps are small and well delineated can be deemed "complete." Various analyses showed that the completed sequence contains less than one error for every 50,000 letters.

Researchers on the chromosome 22 project emphasized yesterday that the results of their work were made freely available to other scientists on the World Wide Web every day as they accumulated. And in

stark contrast to some privately financed efforts—most notably, that of controversial geneticist and entrepreneur J. Craig Venter of Celera Genomics Corp. in Rockville—they said no one on the team had filed for patents on the genes they had found.

WORLD

In Brief

AFRICA

Namibia Awaits Election Results

WINDHOEK, Namibia—Two days of voting ended yesterday in an election almost certain to return the South West Africa People's Organization to power, the only ruling party Namibians have known in a decade of independence.

The southwest African country's biggest opposition party said it was already considering contesting the count because of vote-rigging, though final results aren't expected until Monday. Early results are expected today.

ASIA

Nobel Laureate Returns to E. Timor

DILI, East Timor—Ending 24 years of exile, Nobel Peace laureate Jose Ramos-Horta triumphantly returned to his liberated homeland where thousands of supporters greeted him with chants of "Long live Ramos-Horta!"

"I am overwhelmed—very, very happy," Ramos-Horta said upon arrival in Dili. He played down his role in East Timor's fight for independence from Indonesia, and in an emotional speech, he paid tribute to those who remained in East Timor during the long struggle.

Japanese Cult Admits Blame for Attacks

TOKYO—Aum Shinrikyo, the doomsday cult behind a deadly gassing in Tokyo's subway, took responsibility for a string of attacks and promised compensation, but victims' relatives dismissed it as a self-serving move.

The group had not previously admitted its culpability. Former guru Shoko Asahara is on trial for masterminding at least 17 crimes, including the Tokyo sarin nerve gassing that killed 12 and sickened thousands in March 1995. A number of cult members have been convicted or are still on trial on numerous charges.

The cult's decisions to honor Asahara and resume recruiting has set off protests across the nation. The cult is believed to have some 2,100 followers.

U.N. Official Says No Children in Taliban

KABUL, Afghanistan—A senior U.N. official, challenged by the Taliban to find child warriors in its ranks, said that he found no children fighting for the Islamic militia in a visit to a front line near Kabul.

"What I have seen today gives me the impression that this is not the case. People of seasoned age, middle age and youngsters are there, but not at the age of 14 or 15," said Erick de Mul, the U.N. aid coordinator for Afghanistan.

His statement was at odds with one by U.N. Secretary General Kofi Annan, who issued a report on Afghanistan this week in which he said children under age 14 were in combat alongside the Taliban against opposition fighters.

EUROPE

Irish Republic to Drop Claim to N. Ireland

DUBLIN—Foreseeing permanent peace in Ireland, Prime Minister Bertie Ahern declared his government is firmly committed to dropping its territorial claim on the British-linked north.

Ahern addressed lawmakers in Dublin hours before the British government was scheduled to formally transfer powers to a new Protestant-Catholic government for Northern Ireland. Ahern said the Irish Republic's 1937 constitution would be amended today in keeping with the Good Friday peace accord of 1998. The proposed change, overwhelmingly approved by Irish voters last year, drops the definition of Northern Ireland as "part of the national territory" in favor of proclaiming hope that the north's British Protestant majority might one day seek unification.

In London, Prime Minister Tony Blair announced that Queen Elizabeth II had approved legislation transferring powers to the new Northern Ireland government.

Crash Victims' Families to Get Damages

ROME—Families of the 20 people who died when a U.S. Marine jet clipped a cable car line in the Italian Alps in 1998 will each receive up to \$2 million in damages under a new law approved by Italy's Senate.

The legislation, adopted late Tuesday, names a special commissioner to identify the victims' relatives, determine the damages due and pay out the sum within three months.

Under a NATO convention, the host country pays 25 percent of the damages while the country responsible for the accident pays the remaining 75 percent. The treaty allows nations to try their own military officers, and regulates compensation in accidents involving two NATO nations.

THE MIDDLE EAST

Protesters Urge Release of Iranian Cleric

TEHRAN—Dozens of people gathered outside the home of a senior cleric to demand the release of a leading reformist who was jailed for advocating democracy, residents said.

Abdollah Nouri, a former interior minister and close ally of Iran's moderate president, was sentenced Saturday by a clerical court to five years in prison on charges including religious dissent.

Nouri held some of the top state positions in the Islamic republic, but in prison he is treated like an ordinary prisoner, the pro-reformist Asr-e-Azadegan newspaper reported. He shares a 6½-by-10-foot cell with three other prisoners, all clerics, his lawyer said.

FOR THE RECORD

■ **KIGALI, Rwanda**—Congolese rebels warned the government to halt a massive bombardment, threatening to take revenge against 700 Zimbabwean troops the insurgents have surrounded.

■ **MANAGUA, Nicaragua**—Nicaragua launched an economic and diplomatic offensive against Honduras, breaking commercial ties with its neighbor over a maritime treaty that gives Colombia rights to Atlantic waters claimed by Nicaragua.

■ **TRIPOLI, Libya**—Italian Prime Minister Massimo D'Alema became the first Western head of state to visit Libya since 1992 sanctions isolated the nation, giving a vote of confidence to a country struggling to overcome Western isolation.

QUOTE OF THE DAY

"We have no regrets for these charges. The public supports our petition. Arafat should apologize to us."

— **Hassan Khreisheh**, one of the dissident Palestinian lawmakers who signed a statement accusing Palestinian leader Yasser Arafat of allowing widespread corruption—Page A30

Compiled from news services

The Washington Post

THURSDAY, DECEMBER 2, 1999

Researchers Claim No Error in Gene Therapy Death

By DEBORAH NELSON
and RICK WEISS
Washington Post Staff Writers

A teenager's death during a gene therapy experiment at the University of Pennsylvania was caused by the treatment but not by any errors by the research team, according to the preliminary findings of a two-month internal investigation.

The death is the first attributed to gene therapy, a nine-year-old field of research that is trying to find a way to use genes to over-

come inherited diseases, cancer and other problems.

The findings were disclosed in a brief summary report released yesterday by the researchers who conducted the experiment. The researchers declined to provide the supporting documentation until next week, when they make a public presentation before a federal oversight board looking into the death.

The experiment had been controversial even before the death of Jesse Gelsinger, an 18-year-old Tucson resident, because it test-

ed unusually large doses of a gene-altered virus on relatively healthy volunteers with a rare liver disorder.

"The findings suggest that the experimental drug used in the trial—a modified cold virus, or vector, incorporating a potentially corrective gene for Mr. Gelsinger's genetic disease—initiated an unusual and deadly immune-system response that led to multiple organ failure and death," the report states.

However, the researchers said they still don't know why the virus, known as an adenovirus, triggered a lethal reaction in Gelsinger.

Gelsinger received a significantly larger dose of vector than all but one of the other participants. But there were no early warnings of trouble in the other volunteer who received the high dose or in 16 earlier volunteers who received smaller doses, the report states.

The report acknowledges that some participants suffered temporary liver damage but says a review of patient data and of animal studies performed before the clinical trial "revealed no information that would have predicted the events that led to Mr. Gelsinger's death."

"There was no evidence of human error in his clinical management," the report says.

The Washington Post reported last week that monkeys given a high dose of a genetically engineered virus by the Penn team a few years ago had died in a manner similar to Gelsinger. Penn re-

searchers subsequently developed what they considered to be a safer version of the virus for the experiment.

However, some scientists, citing a growing body of evidence that adenovirus in any form causes serious side effects, have questioned the wisdom of using it to treat genetic diseases. The risk might be warranted if the participants were dying and had exhausted conventional treatments, they said. But the Penn team chose to experiment on adults with a mild form of a liver disorder—ornithine transcarbamylase deficiency—who either suffered no symptoms or had them under control with drugs and diet.

The report states that the researchers were mindful of the potential side effects and "carefully monitored all patients for liver inflammation and/or injury using liver-function tests and liver biopsies. While there was evidence of liver inflammation in some patients, all such episodes proved transitory in nature," and their livers returned to normal within two weeks.

Gelsinger died within four days of receiving the infusion on Sept. 13. His decline began within a day, as he developed a systemic blood clotting disorder followed by respiratory distress and then liver and kidney failure on Sept. 17.

In the investigation that ensued, Penn researchers checked the vector for abnormalities but found none, according to their summary. All laboratory data

that they reviewed pointed to an unusually severe reaction to the genetically altered virus, the report says.

"In the context of this unexpected tragedy, the researchers—Dr. James Wilson, Dr. Steve Raper, and Dr. Mark Batshaw—remain committed to fully evaluating all potential leads," the report states. "The purpose of these efforts is to understand the precise nature of Mr. Gelsinger's unfortunate death, and to share the knowledge gained with the research community and the pub-

lic in order to prevent another such occurrence."

Gelsinger's death prompted the Office of Biotechnology Activities at the National Institutes of Health to call on all researchers using adenoviruses to report any ill effects that might shed light on his death or prevent future injuries.

The results of that solicitation and of the Penn investigation will be presented next week in Bethesda to a special NIH advisory committee that monitors gene therapy experimentation.

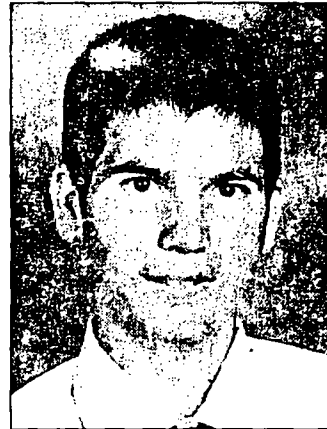
Calls Grow for More Oversight of Gene Therapy

By RICK WEISS
and DEBORAH NELSON
Washington Post Staff Writers

Some scientists, bioethicists and patient advocates are calling for stronger federal oversight of human gene therapy, a fledgling field of promising but unproven medicine that seeks to cure diseases by giving people new genes.

The call for closer scrutiny comes in the wake of recent revelations that biotechnology and pharmaceutical companies have been withholding information about patient deaths in gene therapy experiments, and amid concerns that an 18-year-old's death in a recent Pennsylvania gene therapy study might have been avoided with closer oversight.

"The field is being driven by companies that care about the stock market," said Abbey S. Meyers, president of the National Organization for Rare Disorders in New Fairfield, Conn., who is among those in favor of a larger federal oversight role. "But it doesn't work yet, and the companies aren't being



BY JON WOLFE PHOTOGRAPHY

Jesse Gelsinger, 18, died mysteriously in September in a gene therapy test in Pennsylvania.

honest about the side effects. Families with genetic disease are not being told the truth."

The renewed focus on federal regulation of gene therapy—which may climax in a showdown between federal officials and drug companies at a Dec. 8-10 meeting

at the National Institutes of Health—comes three years after NIH Director Harold Varmus made the controversial decision to scale back his agency's role in reviewing proposed gene therapy studies.

That retreat, which allowed researchers to skip certain layers of scientific and ethical review, was the result of pressure from AIDS patients desperate for novel therapies, and biotechnology companies chafing under what they felt was an overly burdensome regulatory system. Both groups wanted to accelerate gene therapy's transition from a laboratory science to a medical art.

In some ways the streamlining worked: The number of new genetic therapies being tested in people increased immediately and has continued to climb steeply ever since. And while academic researchers dominated the field through the early 1990s, about 40 percent of the new studies proposed in the past three years have had industry sponsors that hope to commercialize genetic cures.

At the same time, however, the Office of Recombinant DNA Activities (ORDA), which oversees gene therapy at the NIH, suffered budgetary and staff reductions and then was given a new range of policymaking responsibilities for such difficult and controversial issues as genetic testing and cross-species organ transplants into people. That has left the office—recently renamed the Office of Biotechnology Activities, reflecting its new responsibilities—hard pressed to manage even the reduced levels of gene therapy oversight that it was left with in 1996, experts outside that office said.

For example, the office is supposed to update and manage a publicly accessible database of every gene therapy experiment in the country, including a description of side effects that researchers have encountered. But the database has not been updated since 1995 "because of a lack of money and support," said A. Dusty Miller, a gene researcher at the Fred Hutchinson Cancer Research Center in Seattle and a former member of the Recombinant DNA Advisory Committee (RAC), the panel of scientists, ethicists and others that reviewed all gene therapy protocols for ORDA before the 1996 cutback.

Now some observers are wondering whether the database might have saved the life of teenager Jesse Gelsinger, who died mysteriously in September while participating in a gene therapy experiment at the University of Pennsylvania. Only after Gelsinger's death did the Penn researchers who directed his treatment become aware that other scientists conducting similar experiments had documented serious side effects.

"It's tragic that the death of one generous young man had to be the occasion for us to see clearly the price we have paid in diminishing the RAC's power and prestige," said Erik Parens, of the Hastings Center, a bioethics think tank in Garrison, N.Y. "Perhaps one significant good that will come of this is that we will rethink the proper place and power of RAC."

James Wilson, the lead gene researcher in the Gelsinger study, was among those who wrote letters to the NIH during the summer of 1996 in favor of reducing RAC oversight—especially its power to

approve or disapprove gene therapy proposals—saying the reduction was necessary "to allow continued evolution of this field in an unencumbered way."

A spokesman for Wilson said yesterday that Wilson is "still committed to the principles" behind the 1996 changes, particularly the principle that all data relevant to the safety of gene therapy should be openly shared. Wilson and his colleagues have been praised by many in the gene therapy world for their immediate disclosure of Gelsinger's death and the provision of details surrounding that tragedy.

But with the NIH database still incomplete and offline—and with some experts concerned that the informed-consent forms that spell out medical risks to gene therapy volunteers may not be getting properly reviewed since the RAC lost its power to approve them—some in Congress are wondering whether the RAC needs to be beefed up again.

Yesterday Rep. Henry A. Waxman (D-Calif.), who opposed the 1996 cutback, was preparing a letter to Varmus expressing anew his concern about the NIH's diminished standing. A spokesman for Sen. Bill Frist (R-Tenn.) yesterday said the senator was still awaiting a reply to his Nov. 4 letter to Varmus addressing similar concerns. An NIH spokesman said a response was being crafted and would be completed "very soon."

Frist's letter cited recent reports that at least seven deaths among participants in gene therapy trials in the past 20 months were not reported promptly to the RAC (some were reported later, but lacking details required by NIH); three addi-

tional deaths were reported, but the scientists or companies submitting the reports tried to keep them from becoming public.

All the deaths were reported to the Food and Drug Administration, which also reviews adverse events but which, unlike the RAC, meets behind closed doors.

Varmus said yesterday that the 1996 cutback did not change the NIH requirement that gene researchers must promptly report all significant adverse events to the RAC. "The rules are there and they're pretty clear," he said.

But some companies have said they will argue against that rule at the upcoming RAC meeting—a meeting at which Wilson will describe the results of Penn's investigation into the cause of Gelsinger's death.

Biotech Crops Spur Warning

30 Farm Groups Say Consumer Backlash Could Cost Markets

By WILLIAM CLAIBORNE
Washington Post Staff Writer

CHICAGO, Nov. 23—More than 30 farm groups across the country today warned their members about the dangers of planting genetically engineered crops, saying the practice had become so unpopular with consumers that farmers were risking their livelihoods if they cultivated them again this year.

The farm groups, which included the National Family Farm Coalition and the American Corn Growers Association, also warned that inadequate testing of gene-altered seeds could make farmers vulnerable to "massive liability" from damage caused by genetic drift—the spreading of biologically modified pollen—and other environmental effects.

The farmers called on chemical companies engaged in bioengineering to promote the sale of traditional seed varieties for the coming crop year until an independent assessment of the environmental, health and economic impacts of gene-altered seeds is available.

In their first coordinated declaration on the potential impact of planting genetically engineered seed, the groups held a teleconference with reporters in Washington in which several Midwestern farmers and the heads of farm groups representing tens of thousands of producers said their chief concern was the marketability of foods created through biotechnology.

Many of the farm groups represented, including Farm Aid, which convened the conference, have been active in the fight to preserve family farming and curtail the growth of corporate agribusinesses.

"Export markets in Europe and Asia are saying 'no' to foods produced from genetically engineered crops [and] farmers know they have to respond to consumer demand if they are to survive," said Gary Goldberg, head of the corn growers association. "Right now, farmers may decide it is best for them to say 'no' to GMO seed." GMO is an acronym for genetically modified organism. Genetically engineered crops contain genes from bacteria and viruses to

make them resistant to insects and weed killers.

Val Giddings, vice president for food and agriculture for the Biotechnology Industry Organization, said it "wouldn't be surprising if there was some slacking off" in the sale of biotechnology seeds this season, but he said the farm groups' market assessment was grossly distorted. "Fears of a market impact are nil," Giddings said. He also said numerous independent studies of bioengineered foods had proved them to be safe.

One farmer at today's news conference, Rodney Skalbeck of Sacred Heart, Minn., said he has planted genetically engineered corn and soybeans on his 750 acres for the last two years but doubts if he will this spring. "There's no problem, except how are you going to sell them?," Skalbeck said. "They haven't told us the truth about what's really happening. Are we going to lose the European market? Are we going to have a market here?"

Other farmers said they were concerned about having to pay premium prices for biotech seeds and then having to sell their crop at a discount, if they can sell it at all. As they prepare to place their seed orders for spring planting, the farmers said they are in a quandary because of the uncertain markets and the spreading controversy over bioengineered foods.

Seed dealers and grain buyers contacted independently before today's news conference said they also have become frustrated trying to anticipate the effects of consumer anxiety over the safety of gene-altered crops. They point out that commodities prices are already depressed by a worldwide glut of some grains, increased foreign competition and shrinking markets abroad.

Some seed dealers said they are bracing for a falloff in anticipated sales of genetically altered seeds, which last year topped \$1 billion nationally and which, according to some estimates, had been expected to double this year.

"I think we're going to see them stepping away from GMOs, particularly corn," said Ken Hintzsche, a dealer in Maple Park, Ill. "I don't

know how much, but there's a lot of concern out there."

Jerry Bertrand, a grain dealer in Grant Park, Ill., said, "Farmers are pretty confused, and with good reason. I can't tell them with any certainty that I'll take their GMO corn and soy next year because I don't know if there'll be a market for it."

Bertrand said that a year ago, most farmers he knows thought that gene-altered seeds were "the next best thing to sliced bread." Now, he said, "all of this misinformation and hysteria is going to hurt the market."

Bertrand said he thought that biotechnology companies such as Monsanto Co. and DuPont Co.'s Pioneer Hi-Bred International Inc., which in recent weeks have been sending representatives to farm regions to reassure producers about the market, "didn't do a very good job of selling this to the public in the first place."

Another grain buyer, Robert Seegers Jr. of Crystal Lake, Ill., said, "I think there's going to be a reluctance to plant [gene-altered] corn. I don't think they'll risk it this year." Seegers said that while he does not agree with the widespread public perception that genetically modified food is unsafe, "often perception is more important than reality."

Dean Urmston, executive vice president of the American Seed Trade Association, said that while it is too early to define a trend, "I do know that our members are concerned because of the emotional things being expressed by the media and others."

To counter the fears, the association has put on its World Wide Web site a grain handlers' database in which farmers can enter their Zip codes and instantly view a list of buyers who will take their genetically altered crops even if they don't meet the safety specifications of the European Union, which has led the resistance against agricultural biotechnology.

Urmston said 80 percent of the U.S. grain crop is purchased domestically and 54 percent of that is bought by about 2,000 grain handlers who say they will accept gene-altered crops. "So, the market is here. . . . Where's the panic?" Urmston asked.

The Washington Post

WEDNESDAY, NOVEMBER 24, 1999

[draft 12/6 noon, LB]

**Message Points for Rick Weiss Interview
December 6, 1999**

- FDA is currently doing an extensive investigation into the gene therapy clinical trial which led to the death of a patient, Jesse Gelsinger, last September.
- Normally, FDA would not comment on specific aspects of an ongoing investigation. But because of the public health significance of gene therapy, and the public interest in the death of a patient, the agency will comment generally on this matter.
- After reviewing summary information provided by the sponsor on all patients enrolled, FDA has concerns about the conduct of this trial.
- Preliminary evidence suggests that there were protocol deviations that involved two areas: patient inclusion and stopping rules.
- It appears that one patient, Jesse Gelsinger, did not meet the entry criteria specified in the clinical research plan. [Results of certain chemical tests did not meet the entry criteria: elevated blood levels of ammonia. (This was disclosed to the News Hour.)]
- Concerning the other deviation, it appears that in other patients the stopping rules were not applied. According to the clinical trial design, the study was to be stopped if a particular level of toxicity was observed. No new patients should have been entered into the trial without the sponsor first consulting with the FDA.

- At this time, it is not clear whether these protocol violations put patients at increased risk in this study. That is a possibility we are still looking into.
- We have also reviewed summary data of the animal tests that have been conducted with the gene therapy vector, including studies that were done after the first patients had received the gene therapy vector. In studies done with the same vector used in the clinical study, at doses approximately 16 times the highest clinical dose, evidence of disseminated intravascular coagulation and liver toxicity was seen in monkeys. Some of this information was not submitted to the agency before the death of the patient. [This information was not disclosed to the News Hour.]

DRAFT TALKING POINTS

SET UP FOR THE RAC MEETING DECEMBER 8-9-10, 1999

December 5, 1999

One purpose of the meeting is to discuss the safety and toxicity of adenoviral vectors in connection with human gene therapy trials.

An adenoviral vector was used in the gene therapy trial in Philadelphia in which a young man died in September 1990.

NIH and FDA are bringing in experts from around the country to discuss this matter in public session.

A second purpose of the meeting is to discuss the prompt reporting by clinical investigators of "serious adverse events" to the FDA and the NIH as is required. Concerns have been raised following the death in Philadelphia about investigators' compliance with NIH guidelines.

The public meeting is expected lead to recommendations about the safety of adenoviral vectors and recommendations for changes in reporting requirements for reporting serious adverse events to the NIH.

December 5, 1999

Although gene therapy research, like any form of clinical research, poses potential risks to research subjects, we are committed to minimizing risks & ensuring that patients are fully informed of such risks.

As gene therapy research develops, so does our knowledge about the risks associated with it. To this end, we make every effort to make certain that the gene therapy clinical trials we support are safe & in conformance with Federal guidelines & regulations.

Questions and Answers
Regarding
Adverse Event Reporting in Gene Transfer Clinical Trials

QUESTION: What are the current NIH requirements for the reporting of serious adverse event, including patient deaths on gene therapy protocols?

The *NIH Guidelines* 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 such techniques. The requirements for reporting serious adverse events in human gene transfer research are found at Appendix M-VII-C in the *NIH Guidelines*. Appendix M-VII-C states:

Investigators who have received approval (authorization) from FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety Committee, Office for Protection from Research Risks (if applicable), NIH ORDA, and FDA, followed by the submission of a written report filed with each group. Reports submitted to NIH ORDA shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSB 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, 301-496-9838.

As stated in Section I-D of the *NIH Guidelines*, noncompliance may result in: (i) suspension, limitation or termination of NIH funds for the gene therapy project at issue or for all recombinant DNA research at the institution or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution (i.e., in order to continue to receive NIH funds for recombinant DNA research, an institution could be required to obtain NIH approval prior to initiation of any or all individual research projects and clinical trials involving recombinant DNA).

QUESTION: Recent press accounts report that some investigators conducting gene therapy research have not reported to NIH serious adverse events, including patient deaths. Was the NIH informed of the patient deaths reported in the press?

Five of the six serious adverse events (deaths) described in the November 3, 1999, edition of the *Washington Post* were not reported to the NIH as required by *NIH Guidelines*. One of the six serious adverse events was reported but labeled confidential by the investigator, thereby precluding a public discussion of this adverse event. Serious adverse events are required to be reported to the NIH immediately.

QUESTION: In the recent report of a death at the University of Pennsylvania, did the investigator comply with the *NIH Guidelines*?

This adverse event was reported immediately to the NIH, with no claim of confidentiality.

QUESTION: What steps is NIH taking to understand the implications for the field of gene transfer research of the patient death in the University of Pennsylvania protocol?

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. In an effort to stimulate broad public discussions and scientific analysis of this adverse event, the NIH/RAC will hold a scientific symposium and meeting on December 8-10 to conduct a comprehensive review and discussion of the data.

QUESTION: What is NIH planning to do to ensure that gene therapy researchers understand the legal requirements and regulations for reporting of patient deaths?

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 has been sent to all Institutional Review Boards, Institutional Biosafety Committees, and Principal Investigators at institutions conducting human gene transfer studies.

The NIH and FDA have established a new serious adverse event notification process whereby FDA notifies the NIH when it receives serious adverse event reports from investigators and sponsors. One of the main goals of 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.

QUESTION: What is NIH doing to ensure that serious adverse events reports to the RAC are not classified as confidential, trade secrets or proprietary information?

The NIH is amending the *NIH Guidelines* to increase compliance with the reporting requirements. A proposed action to amend the *NIH Guidelines* was published in the November 22, 1999, *Federal Register* for public comment and will be discussed at the upcoming RAC meeting on December 8-10, 1999. The proposed action will 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.

QUESTION: What other steps is NIH taking to determine whether further actions need to be taken to ensure the safe and ethical conduct of clinical gene transfer research?

As part of NIH's response to recent events, the NIH Director established a working group of the Advisory Committee to the Director, NIH to review comprehensively and in public session the role of NIH in oversight of clinical gene transfer research. From its comprehensive review, the Working Group will be asked to develop recommendations and report back to the Advisory Committee to the Director, NIH.

In addition, the NIH and FDA have initiated 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.

December 3, 1999

Q's and A's Based on November 21, 1999 Washington Post Article**"Hasty Decisions in the Race to the Cure"****1. Can you describe the process for FDA's oversight of clinical trials involving gene therapy and the role of the clinical investigator?**

- The investigational new drug application (IND) submitted to FDA is reviewed by medical and scientific reviewers who assess product safety, pre-clinical studies and justification for the trial, and the design of the clinical protocol.
- There is additional oversight by the local institutional review board (IRB), which assures that appropriate informed consent and protection of human subjects has been obtained by the investigators.
- There is also oversight by the local Institutional Biosafety Committee and the local Institutional Animal Care and Use Committee.
- When FDA is satisfied that issues have been addressed, the FDA allows the protocol to proceed.
- Once FDA authorization is obtained, the clinical study cannot proceed until the local IRB approves the trial.
- The day-to-day conduct of the trial is the responsibility of the sponsor, who administers the protocol and assures that adverse events and rules for stopping the protocol are obeyed.
- The local investigator monitors patient responses and is responsible for the evaluation of the clinical condition of the patients.
- The local investigator also has current medical information on each patient, and evaluates the criticality of the patient's condition and the relationship of adverse events to product administration.
- **Unexpected fatal or lifethreatening adverse experiences** associated with an investigational drug are required to be reported within seven days to FDA. In this particular case, the investigator, the local IRB and the FDA all halted the clinical trial at the time of the patient's death.

2. **Why didn't FDA stop Dr. Wilson as he suggested if it were so dangerous?**

- FDA extensively reviewed Dr. Wilson's proposed research, as well as commentary from the RAC.
- FDA required additional animal safety experiments and revisions to the protocol intended to improve the safety of the study.
- The protocol as approved by FDA included many safety features:
 - Tests on prospective patients to exclude those at high risk for toxicity;
 - Tests on subjects to detect toxicity; and
 - Stopping rules intended to halt the study after significant toxicity was observed to avoid placing additional patients at risk.
- FDA believed at the time and still believes that this protocol had sufficient safeguards to allow it to proceed.

3. **Was the protocol followed? What went wrong?**

- The A thorough investigation is underway and we cannot, at present, comment on specifics.
- However, we have concerns over the conduct of this trial. (Following a review of summary information provided by the sponsor on all patients entered in this IND,) it appears that the stopping rules concerning adverse events were not followed in two cases, and that one patient did not meet one of the entry criteria.
- At this time, it is not whether these protocol violations put patients at extra risk in this study.
- We have also reviewed summary data of the animal tests that have been conducted with the gene therapy vector, including studies that done after the first patients had received the gene therapy vector. In studies done with the same vector used in the clinical study, at doses approximately 16 times the highest clinical dose, evidence of disseminated intravascular coagulation and liver toxicity was seen in monkeys. Some of this information was not submitted to the agency before the death of patient number 19.

4. Why did FDA change the route of administration?

- After the December 1995 RAC discussion, FDA subsequently received the proposal to use intravenous (iv) rather than intra-arterial administration of vector.
- We required new animal safety tests be done to show not only the safety of the iv route, but also to examine whether the adenoviral vector would be disseminated to gonadal tissue of the animals.
- The animal studies performed by the investigators showed that the safety profile was similar for both iv and intrahepatic-arterial routes; however the iv route reproducibly led to extensive and extended gonadal distribution of the vector and a higher distribution to many organs.
- In contrast, the intrahepatic-arterial route showed little vector dissemination to the gonads. Since many of the patients would be females with the potential for having children, FDA felt that the animal data available at that time warranted the intrahepatic-arterial route of administration.
- In addition, based on these animal studies, there was reason to believe the intrahepatic-arterial route was safer. Not only are gonads and other tissues less exposed, by infusing only part of the liver, but the remainder of the liver is less exposed, which could be very helpful in case of toxicity.
- The fact that toxicity occurred equally in both the infused lobe and the non-infused lobe suggests strongly that the route of administration was not the cause of the problem.
- FDA has several protocols (non-gene therapy as well as gene therapy) that use intrahepatic-arterial injections. The risk from arterial injection seems to be quite limited.
- The RAC recommendation regarding iv versus intrahepatic-arterial administration was based on concerns relating to risks of intrahepatic-arterial catheterization. The RAC explicitly noted that there was no reason to believe the gene therapy was safer by the iv route.
- In June of 1999, FDA and the RAC decided that a low risk of inadvertent germ line alteration was acceptable in some phase 1 trials.

5. **Why would FDA conclude that because humans are so much bigger than monkeys, a lower dose could be delivered safely to humans with no minimal side effects?**

- Animal studies are used to determine the first dose that goes into humans. Size adjustments are always made, and because of differences between humans and animals, an additional safety factor is always added.
- Once human studies have begun, the human safety data is also used to determine the study dose. Initial doses are low and dose progression occurs only when earlier doses have been tolerated sufficiently well.
- In the case of this particular trial, a large safety factor was used that was based on the primate models. The first dose levels used in humans appears to have been safe and well tolerated.

6. **Why didn't FDA notify the RAC?**

- ☐ From December 1995 to December 1996 the RAC was in transition from focusing on review of each gene therapy protocol to focusing on broader gene therapy issues.
- In December 1996, the RAC recommended that, because of FDA regulations that might restrict access to information, the investigator should be responsible for reporting to the RAC changes stipulated by the RAC and changes to the protocol mandated by FDA. This recommendation became part of the Recombinant DNA Guidelines on October 31, 1997 by announcement in the Federal Register.
- In addition to the NIH requirements as above, FDA is currently developing procedures to expand communications with the RAC.
- FDA has, and will continue to work closely with the newly renamed Office of Biotechnology Activities at NIH and with the RAC to achieve an appropriate balance of public discussion and disclosure that will ensure and enhance the protection of human subjects in gene therapy trials.

7. **Why did the informed consent change, and why didn't FDA know about it?**

- FDA received the original informed consent document, in which it was stated that in some pre-clinical experiments, non-human primates died as a result of vector administration.
- FDA did not receive any further changes to that informed consent.
- The sponsor has indicated that all changes to the informed consent were approved by the local IRB.

8. a. Should the current process be re-examined for reporting major adverse events in gene therapy studies to the RAC and also ensure that any such events are also promptly and publicly disclosed?
- b. Should the relationship of the public RAC review process for gene therapy protocols to the FDA review process be re-examined?
- FDA appreciates the value of public disclosure and discussion and supports efforts to increase it.
 - FDA has, and will continue to work closely with the newly renamed Office of Biotechnology Activities (OBA) at NIH and with the RAC to achieve an appropriate balance of public discussion and disclosure that will ensure and enhance the protection of human subjects in gene therapy trials. Specifically:
 - FDA issued a letter to gene therapy sponsors on November 5, 1999, to reiterate the preferred timelines for submission of protocols for review to OBA and to FDA, and to remind sponsors of their obligations to report adverse events to OBA.
 - This letter also notes that for those protocols deemed novel for public discussion, the RAC discussion should take place before submission of the IND to FDA. This will insure that changes stipulated by the RAC discussion are incorporated prospectively.
 - FDA is examining other ways for expanding communication with OBA.
 - While the role of RAC in providing public, scientific overview is critical; the RAC does not have regulatory authority. FDA has legal authorities such as prohibiting research with specific products and taking sanctions against investigators who do not comply with regulations.
 - FDA scientists address newly arising issues in IND protocols on a daily basis; a responsiveness that is critical in a field changing as rapidly as is gene therapy.

**National Institutes of Health
Recombinant DNA Advisory Committee (RAC) Symposium and Meeting
December 8-10, 1999, Bethesda, Maryland
Agenda¹**

****Please Note Location for Each Day****

**December 8, 1999 - RAC Symposium
National Institutes of Health
Building 10, Masur Auditorium**

- I. Call to Order and Opening Remarks/Mickelson 8:00 a.m.**
NIH Opening Remarks/Patterson 8:05 a.m.
- II. Keynote: Adenovirus Biology, Pathophysiology and Adaptation to Gene Therapy 8:10 a.m.**
Adenovirus Molecular Biology and Disease 8:10 a.m.
Marshall Horwitz, M.D., Albert Einstein College of Medicine

Adaptation of Adenovirus for Gene Transfer 8:25 a.m.
Inder Verma, Ph.D., Salk Institute
- III. Examples of Adenovirus-induced Pathophysiology 8:40 a.m.**
Moderator: Inder Verma, Ph.D., Salk Institute

The Interplay Between Adenovirus and Pro-inflammatory Cytokines 8:45 a.m.
Linda Gooding, Ph.D., Emory University

Receptors and Signaling Events in Adenovirus Cell Entry 9:00 a.m.
Glen Nemerow, Ph.D., Scripps Research Clinic

Adenovirus-induced Hepatotoxicity 9:15 a.m.
Robert Warren M.D., University of California, San Francisco

Disseminated Intravascular Coagulation 9:30 a.m.
Margaret Rick, M.D., NIH

Estuardo Aguilar-Cordova, Ph.D., Baylor College of Medicine. 9:45 a.m.

Helper Dependent Adenoviral Vector -- Development, Performance and Safety 10:00 a.m.
C. Thomas Caskey, M.D., Merck & Company, Inc.
- IV. Safety and Toxicity Data from Clinical Trials Using Adenoviral Vectors 10:15 a.m.**
Moderator: Inder Verma, Ph.D., Salk Institute for Biological Studies

Summary of Phase I Studies with Adenoviral Vectors at Penn 10:20 a.m.
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¹All times on this agenda are estimates. The actual time for consideration of an item may be earlier or later than indicated.

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James Wilson, M.D., Ph.D., University of Pennsylvania

Safety of Local Delivery of Low and Intermediate Dose Adenovirus Gene Transfer Vectors to
Individuals with a Spectrum of Comorbid Conditions. 10:35 a.m.
Ronald Crystal, M.D., Cornell Medical Center

David P. Meeker, M.D., Genzyme Corporation 10:50 a.m.

JoAnn Horowitz, Ph.D., Schering-Plough 11:05 a.m.

Ad5CMV-p53 (RPR/INGN 201) - Global Safety Assessment 11:20 a.m.
Lyndah K. Dreiling, M.D., Gencell/Rhone-Poulenc-Rorer

David H. Kim, M.D., Onyx Pharmaceuticals 11:35 a.m.

TBA 11:50 a.m.

Lunch Break 12:05 p.m.

Panel Discussion 1:05 p.m.

Public Comment 1:35 p.m.

Working Group Discussion and Synopsis 1:50 p.m.

Tab 2097 Comment from Public Page 1074

V. End of Session/Mickelson 3:00 p.m.

**December 9, 1999 - RAC Meeting
National Institutes of Health
Building 10, Masur Auditorium**

VI. Opening Remarks/Mickelson 8:30 a.m.

Tab 2087 Notice of Meeting Page 10
 Proposed Actions Page 11
Tab 2094 Rules for Conflict of Interest (FACA) Page 1030

VII. Discussion of Ornithine Transcarbamylase Deficiency Protocol 8:45 a.m.

Presentation of Severe Adverse Event on Human Gene Transfer Protocol #9512-139 entitled:
*A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial
Ornithine Transcarbamylase Deficiency (OTC)* 8:45 a.m.
Investigator: Mark Batshaw, M.D., Children's National Medical Center, D.C.
Co-Investigator: James Wilson, M.D., University of Pennsylvania
Contact: Philip J. Cross, University of Pennsylvania

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Tab 2089	RAC Minutes on OTC Protocol, 12/4-5/95	Page 158
	Article on Adenovirus, <i>Human Gene Therapy Journ</i> , 9/20/98	Page 169
	Article on OTD, <i>Medical Intelligence</i> , 10/13/88	Page 177
	Protocol, <i>Human Gene Therapy Journal</i> , 9/20/99	Page 182
	Report of Serious Adverse Event, 9/20/99	Page 201
	ORDA Ltr to RAC, IBC, FDA, OPRR, 9/21/99	Page 204
	FDA Ltr to ORDA, 9/30/99	Page 212
	ORDA Ltr to PI, 10/1/99	Page 213
	Current Informed Consent Document, Rec'd 11/18/99	Page 220
Food and Drug Administration Comments 9:45 a.m.		
Philip Noguchi, M.D.		
RAC Working Group Comments on Human Gene Transfer Protocol #9512-139 10:30 a.m.		
Discussion Co-Chairs Markert and Chabner		
Public Comment 11:30 a.m.		
Lunch Break 12:00 noon		
RAC Working Group Recommendations on Adenovirus-Safety and Toxicity 1:15 p.m.		
● Preliminary Findings and Conclusions		
● Time Line for Issuance of Final RAC Report		
Discussion Co-Chairs: Mickelson and Horwitz		
Public Comment 2:45 p.m.		
VIII.	Data Management/Greenblatt 3:30 p.m.	
Tab 2088	Protocol List	Page 17
	Protocols Not Requiring Full RAC Review	Page 68
Tab 2098	Safety Reports and Adverse Events	Page 1077
	Amendments and Updates	Page 1084
IX.	Minutes of the September 2-3, 1999, Meeting 4:00 p.m.	
	Reviewers: Greenblatt, Juengst	
Tab 2099	RAC Minutes/September 1999	Page 1094
X.	End of Session 4:45 p.m.	

December 10, 1999-RAC Meeting
National Institutes of Health
Natcher Building 45, Room E1 & E2

XI.	Opening Remarks/Mickelson 8:30 a.m.
XII.	Current Issues in Adverse Event Reporting 8:35 a.m.
	Working Group Participants: Macklin

Page 4 - RAC Agenda - December 8-10, 1999

FDA Presentation on Adverse Events Reporting 8:45 a.m.
Questions and Answers 8:55 a.m.

NIH Presentations on Adverse Event Reporting 9:05 a.m.
Questions and Answers 9:15 a.m.

XIII. Proposed Action on Adverse Event Reporting 9:35 a.m.

Working Group: Chair: Macklin

Members: McIvor, Ando, King, Verma

Tab 2087	Proposed Actions	Page 11
Tab 2093	FDA Support Letter on Public Review, 9/30/99	Page 1021
	FDA Letter to IND Sponsors & PIs, 11/5/99	Page 1022
	Letter from Walters, et.al., 11/5/99	Page 1024
	ORDA's Serious Adverse Event Reporting Form	Page 1026
	ORDA's Letter on Reporting Adverse Events, 11/22/99	Page 1027
Tab 2096	Comments from Public	Page 1061

XIV. Patient Privacy and Confidentiality 10:35 a.m.

Lana Skirboll, Ph.D., NIH/OSP 10:35 a.m.

Presentation, *To Be Confirmed* 11:05 a.m.

RAC Discussion of Adverse Event Reporting, Patient Privacy and Confidentiality 11:35 a.m.

Public Comment 12:05 a.m.

Lunch Break 12:45 p.m.

XV. Discussion on Human Gene Transfer Protocol #9906-322 entitled: *NGF*

***Ex Vivo Gene Therapy for Alzheimer's Disease* 1:30 p.m.**

Investigator: Mark Tuszynski, M.D., Ph.D., University of California at San Diego

Reviewers: Chow, Mickelson, King

Ad hoc: Wilma Friedman, Columbia University

Tab 2091	ORDA Summary	Page 345
	ORDA Letter to PI on RAC Public Review	Page 349
	RAC Members Recommendations	Page 350
	Review from Chow, Mickelson, King, Friedman	Page 352
	Protocol	Page 366
Tab 2100	PI's Response to Chow, Mickelson, King, Friedman	Page 1126
	King/Additional Comments	Page 1155

- XVI. Discussion on Human Gene Transfer Protocols #9910-342 and #9910-343 entitled: *Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B for the Treatment of a Diabetic Insensate Foot Ulcer and Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B and Limb Compression Bandage for the Treatment of Venous Leg Ulcer (Trial A)* 2:30 p.m.**

Investigators: David J. Margolis, M.D., University of Pennsylvania
Sponsor: Philip J. Cross, Institute for Human Gene Therapy, University of Pennsylvania
Reviewers: Markert, Ando, Macklin

Tab 2092	ORDA Summary	Page 591
	ORDA Letter to PI on RAC Public Review	Page 597
	RAC Members Recommendations	Page 598
	Review from Markert, Ando, Macklin	Page 602
	Protocol #9910-342	Page 608
	Protocol #9910-343	Page 688
Tab 2101	Sponsor's Response to Markert, Ando, Macklin	Page 1160

- XVII. Other RAC Issues 3:30 p.m.**

- XVIII. Chair's Closing Remarks/Mickelson 4:55 p.m.**

- XIX. Future Meeting Dates, Announcements/Mickelson 4:59 p.m.**

Tab 2095	RAC/March 9-10, 1999, NIH, 31C, CR10	Page 1051
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- XX. Adjournment/Mickelson 5:00 p.m.**

● **For Your Information**

Tab 2094	RAC Follow-up	
	--#9902-284/Ragni, ORDA Letter to PI, 9/29/99	Page 1031
	--#9902-284/Ragni, PI Letter to ORDA, 9/30/99	Page 1034
	--#9905-317/Mendell, ORDA Letter to PI, 9/29/99	Page 1044
	FDA Guidance for Retroviral Vectors, 11/3/99	Page 1048

- **Human Gene Transfer Protocol #9908-334 entitled: *A Phase I Study of FGF2-Fab' Modified Adenovirus Vector Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir in Previously Treated Ovarian and Extraovarian Patients***

Investigators: Ronald D. Alvarez, M.D., Mack N. Barnes, M.D., David T. Curiel, M.D.,
University of Alabama at Birmingham
Reviewers: Breakefield, McIvor, Levi-Pearl

Tab 2090	ORDA Summary	Page 232
	ORDA Letter to PI on RAC Public Review	Page 235
	RAC Members Recommendations	Page 236
	Review from Breakefield, McIvor, Levi-Pearl	Page 237
	Protocol	Page 242
Tab 2102	PI e-mail/Protocol Withdrawn	Page 1167

Billing Code 4140-01-P
Federal Register: November 22, 1999 (Volume 64, Number 224)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Office of Recombinant DNA Activities;
Recombinant DNA Advisory Committee
Proposed Actions Under the NIH Guidelines



Agency:
 National Institutes of Health (NIH), PHS, DHHS.

Action:
 Notice of Proposed Actions Under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*.

Summary:
 The purpose of this document is to inform the public of proposed changes to the *NIH Guidelines* related to the reporting of serious adverse events involving human gene transfer research. This notice describes a proposed action to amend the *NIH Guidelines* regarding the reporting and public disclosure of serious adverse events.

Dates:
 The public is encouraged to submit written comments on these proposed changes to the NIH Office of Recombinant DNA Activities (ORDA). Written comments may be submitted to NIH/ORDA in paper or electronic form. Written comments received by December 3, 1999, will be reproduced and distributed to the RAC for consideration at its December 8-10, 1999, meeting.

All comments received in response to this notice will be considered by the NIH and will be available for public inspection in the NIH/ORDA office weekdays between the hours of 8:30 a.m. and 5 p.m.

For Further Information Contact:
 If you have questions, or require additional information about these proposed changes to the *NIH Guidelines*, please contact the Office of Recombinant DNA Activities (ORDA) by e-mail at: ci4e@nih.gov, or telephone at: 301-496-9838. Written comments on these proposed changes to the *NIH Guidelines* can be submitted by e-mail to: ci4e@nih.gov, fax to: 301-496-9839, or mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, MD 20892-7010.

For additional information about the December 8-10, 1999, RAC meeting at which these proposed changes will be deliberated, please visit the NIH/ORDA web site at: <http://www.nih.gov/od/orda>.

Supplementary Information:

Appendix M-VII-C of the *NIH Guidelines* requires Principal Investigators (or their designated sponsors) to report serious adverse events immediately to the local Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), Office for Protection from Research Risks (OPRR) (if applicable), NIH/ORDA, and Food and Drug Administration (FDA).

All non NIH funded projects involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH support for projects involving such techniques must comply with the *NIH Guidelines*. Noncompliance may result in: (i) Suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

All gene transfer clinical studies are subject to FDA regulations found in volume 21 of the Code of Federal Regulations (CFR), including specific requirements at 21 CFR 312.32 related to adverse events.

The immediate reporting of serious adverse events to NIH/ORDA by investigators allows rapid notification of the RAC. This, in turn, allows notification, as appropriate, of other IBCs, IRBs, and Principal Investigators in the field. Immediate reporting also provides a unique mechanism for early recognition of trends in the occurrence of serious adverse events that may raise significant implications for the safety of patients enrolled in similar human gene transfer studies. For example, there have been several instances in which public RAC discussion of serious adverse events has resulted in important changes in the design of vectors for gene delivery. When deemed appropriate, NIH/ORDA will initiate additional data collection for a comprehensive and public review by the RAC and *ad hoc* experts. This process fosters broad public awareness of issues and developments in human gene transfer research. The comprehensive public review of data by the RAC is a critical component of Federal oversight of gene transfer research.

Recently some investigators and sponsors have begun to designate human gene transfer protocols or serious adverse event reports confidential, thereby precluding public RAC review. Out of concern about this development, the NIH requested that the RAC consider whether the requirement for serious adverse event reporting as set forth in the *NIH Guidelines* needed to be clarified.

During the September 2-3, 1999, meeting, the RAC developed the following consensus statement with regard to serious adverse event reporting to NIH/ORDA and the RAC: "Adverse event reports shall not be designated as confidential, either in whole or in part. Adverse event reports are essential to

decision making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports must be made available for public discussion [by the RAC] without the inclusion of proprietary or trade secret information."

Some investigators have not complied with the *NIH Guidelines* requirement to report serious adverse events immediately to NIH/ORDA. While the *NIH Guidelines* are clear on this matter, the NIH is proposing to amend the *NIH Guidelines* to restate the requirements for serious adverse event reporting and to include: (1) A definition of serious adverse events and a stipulation of the time-frame in which they are to be reported in writing (adapted from 21 CFR 312.32 IND Safety Reports); (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 Appendix M-VII-C will be considered public unless NIH/ORDA determines that there are exceptional circumstances; and (3) a directive that serious adverse event reports submitted to ORDA be stripped of individually-identifiable patient information.

Proposed Amendments to the *NIH Guidelines*

A new Section I-E-7 is added to read:

"Section I-E-7. A "serious adverse event" is defined as any expected or unexpected adverse event, related or unrelated to the intervention, occurring at any dose that results in any of the following outcomes; death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into One or More Human Subjects (Points to Consider)

Appendix M-VII-C, Serious Adverse Events, is proposed to read:

"Appendix M-VII-C-1, Serious Adverse Event Reporting

"Principal Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report

immediately in writing any serious adverse event (as defined in Section I-E-7) to the local Institutional Review Board, Institutional Biosafety Committee, Office for Protection from Research Risks (if applicable), NIH/ORDA, and FDA.

"Serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential as defined under the Freedom of Information Act, 5 U.S.C. 552; therefore, unless NIH/ORDA determines that there are exceptional circumstances, all information submitted in accordance with Appendix M-VII-C will be considered public.

"Reports of serious adverse events may be submitted by e-mail to: ci4e@nih.gov, fax to: 301-496-9839, or by mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, MD 20892-7010.

Appendix M-VII-C-2, Serious Adverse Event Reporting: Content and Format

"Reports of serious adverse events must follow the format provided in the Adverse Event Reporting Form available on NIH/ORDA's web site at <http://www.nih.gov/od/orda>. The serious adverse event report must include, but need not be limited to: (1) The date of the event; (2) a complete description of the event; (3) relevant clinical observations; (4) relevant clinical history; (5) relevant tests that were or are planned to be conducted; (6) the suspected cause of the event; (7) gene delivery method; (8) vector type, e.g., adenovirus; (9) vector subtype, e.g., type 5, relevant deletions; (10) dosing schedule; (11) route of administration; (12) clinical site; (13) principal investigator(s); (14) NIH Protocol number; and (15) Investigational New Drug (IND) number.

"Serious adverse event reports should be stripped of individually-identifiable patient information. Examples of such information include, but are not limited to, the patient's name, address, contact information, social security number, date of birth.

Appendix M-VII-C-3, Time-Frames for Serious Adverse Event Reporting: Initial and Follow-Up Reports

"Immediate reporting of serious adverse events is essential for the early identification of acute events related to a gene transfer procedure, as well as the identification of patterns that may signal potential safety concerns. For the purposes of the *NIH Guidelines*, 'immediate' written reporting of all serious adverse events is to occur as soon as possible but no later than 15 calendar days after such an event has occurred. This applies to all serious adverse events, related or unrelated to gene transfer, which occur during the course of the clinical trial.

"Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. The Principal Investigator(s) must provide any relevant follow-up information to a serious adverse event report within 15 calendar days of receipt of the relevant information. In addition, if a serious adverse event occurs after the end of a clinical trial, and is determined to be related to gene transfer, that event shall be reported by the Principal Investigator within 15 calendar days of the determination."

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the *NIH Guidelines*. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Date: November 16, 1999

Lana R. Skirboll, Ph.D.
Associate Director for Science Policy
National Institutes of Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES**National Institutes of Health****Office of Recombinant DNA Activities;
Recombinant DNA Research:
Proposed Actions Under the NIH
Guidelines**

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

SUMMARY: The purpose of this document is to inform the public of proposed changes to the NIH Guidelines related to the reporting of serious adverse events involving human gene transfer research. This notice describes a proposed action to amend the NIH Guidelines regarding the reporting and public disclosure of serious adverse events.

DATES: The public is encouraged to submit written comments on these proposed changes to the NIH Office of Recombinant DNA Activities (ORDA). Written comments may be submitted to NIH/ORDA in paper or electronic form. Written comments received by December 3, 1999, will be reproduced and distributed to the RAC for consideration at its December 8–10, 1999, meeting.

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FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional information about these proposed changes to the NIH Guidelines, please contact the Office of Recombinant DNA Activities (ORDA) by e-mail at: ci4e@nih.gov, or telephone at: 301–496–9838. Written comments on these proposed changes to the NIH Guidelines can be submitted by e-mail to: ci4e@nih.gov, fax to: 301–496–9839, or mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010.

For additional information about the December 8–10, 1999, RAC meeting at which these proposed changes will be deliberated, please visit the NIH/ORDA web site at: <http://www.nih.gov/od/orda/>.

SUPPLEMENTARY INFORMATION: Appendix M–VII–C of the NIH Guidelines requires Principal Investigators (or their designated sponsors) to report serious

adverse events immediately to the local Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), Office for Protection from Research Risks (OPRR) (if applicable), NIH/ORDA, and Food and Drug Administration (FDA).

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to NIH/ORDA and the RAC: "Adverse event reports shall not be designated as confidential, either in whole or in part. Adverse event reports are essential to decision-making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports must be made available for public discussion [by the RAC] without the inclusion of proprietary or trade secret information."

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Dated: November 16, 1999.

Lana Skirboll,

Associate Director for Science Policy,
National Institutes of Health.

[FR Doc. 99-30342 Filed 11-19-99; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[CA-066-99-1990-00; CACA-20139 and CACA-22901]

Notice of Availability of Supplemental Environmental Impact Statement and Preferred Action for the Proposed Sand and Gravel Mining Operation, Los Angeles County, CA

AGENCY: Bureau of Land Management, Department of the Interior, Palm Springs-South Coast Field Office, Desert District, California.

ACTION: Notice of availability of supplemental environmental impact statement and identification of preferred action.

SUMMARY: In compliance with the National Environmental Policy Act (NEPA) of 1969 and 40 CFR 1503.1(a), notice is hereby given that the Bureau of Land Management (BLM) has prepared a supplement to the Draft Environmental Impact Statement (EIS). This supplement to the Draft EIS addresses a new proposal by Transit Mixed Concrete Company to transport mine material by a conveyor belt system rather than open trucks as proposed in the original draft EIS. The supplement will provide; further analysis of the potential air quality impacts. In addition the supplement identifies the BLM's preferred action. Interested citizens are invited to review the Supplement and submit comments. Copies of the Supplement may be obtained by telephoning or writing to the contact person listed below. Public reading copies of the Supplement are available at the following County of Los Angeles public libraries: Canyon County Library, 18536 Soledad Canyon Road, Santa Clarita, CA 91351; Newhall Library, 22704 W. Ninth Street, Santa Clarita, CA 91321; Valencia Library, 23743 W. Valencia Boulevard, Santa Clarita, CA 91355.

DATES: Comments must be received in writing to the BLM no later than January 10, 2000.

ADDRESSES: Written comments shall be mailed to the following address: Mr. James G. Kenna, Field Manager, Bureau of Land Management, Palm Springs-South Coast Field Office, 690 W. Garnet Avenue, PO Box 1260, North Palm Springs, California, 92258. Comments may also be submitted by electronic mail (E-mail) to the following address: emisquez@ca.blm.gov. The response to comments will be provided in the Final EIS.

FOR FURTHER INFORMATION CONTACT: Ms. Elena Misquez, BLM, Palm Springs-South Coast Field Office, PO Box 1260, North Palm Springs, CA 92258, telephone 760-251-4804.

Dated: November 12, 1999.

Carole Levitzky,

Assistant District Manager, External Affairs.
[FR Doc. 99-30094 Filed 11-19-99; 8:45 am]

BILLING CODE 4310-40-M

WHITE HOUSE DOMESTIC COUNCIL MEETING EXECUTIVE SUMMARY

Date: December 6, 1999

Time: 2:00-3:00 p.m.

Subject: Gene Therapy

Background:

Human gene therapy is defined as the administration of genetic material in order to modify or manipulate the expression of a gene product or to alter the biological properties of living cells. Cells may be modified ex vivo for subsequent administration or altered in vivo by gene therapy products given directly to the subject. The original rationale for gene therapy was to treat genetic diseases by replacing a defective gene. For example, lack of adenosine deaminase expression leads to severe combined immunodeficiency (SCID) where the patient cannot mount an immune response to common infections. As the field has developed, in 1999 gene therapy studies are examining a broad range of potential therapeutic interventions, including augmenting tumor specific immune function as well as direct cytotoxic and cytolytic action on tumors, inducing new blood vessels in the heart and legs to alleviate vascular insufficiency, and interfering with HIV replication in AIDS patients. There is also renewed emphasis on genetic diseases such as hemophilia.

Human gene therapy products represent one of the fastest growing areas of product development under FDA oversight, since the Agency first announced in 1993 that cell and gene therapies were subject to regulation under the PHS and FD&C acts (Tab A). Gene therapy products and their uses constitute a new and emerging scientific area that challenges existing regulatory systems, and also present extraordinarily 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. In the five year period 1989 to 1993, 48 new gene therapy INDs were submitted to FDA. Since the 1993 Federal Register notice, 229 new INDs have been submitted, with 54 submitted in fiscal year 1999 (Tab B). As of November 23, 1999, 204 of the 279 submitted are still active, with over 2,000 supplements to these INDs submitted each year.

With the sustained increases of gene therapy IND submissions, FDA has examined ways to reduce the number of duplicative trials, to improve the quality of submitted protocols, and to provide substantive guidance and standards to facilitate preparation of INDs. 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.

To ensure that academic investigators have access to gene therapy vectors for clinical study, three National Gene Vector Laboratories (NGVL) have been funded by the National Center for Research Resources at NIH. To ensure rapid deployment of such services, FDA serves as liaison to this group to make certain that all vectors produced meet FDA requirements. This collaboration has led to increased funding for the NGVL, and all of the facilities are approaching full GMP compliance for vector production.

Public Oversight:

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, with sole authorization to allow clinical trials assigned to FDA, and have agreed to hold public prospective discussions designated Gene Therapy Policy Conferences (GTPC) on major ethical issues such as in utero and germline gene therapy protocols. 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 (Tab C).

The first joint GTPC under this collaboration discussed cosmetic gene therapy, which engendered wide public discussion and interest. Subsequent GTPC have focused on discussions of the biology of lentiviral vectors and most recently the scientific and ethical considerations surrounding potential in utero gene therapies. These conferences have greatly enhanced FDA's credibility in terms of its oversight of gene therapy protocols.

FDA recently brought to the RAC a series of questions on the risks of gonadal vector distribution in phase 1 studies because of the increasing number of gene therapy INDs put on clinical hold because of preclinical findings of persistent vector signal in gonadal tissues. The public and the RAC discussion allowed FDA to remove the clinical holds on a number of the phase 1 protocols (Tab D). In order to increase public knowledge of adverse events, FDA and OBA have taken steps to remind sponsors of their reporting requirements to both FDA and OBA, and OBA has proposed that adverse event reporting be made consistent with current FDA requirements (Tab E, F).

Ornithine Transcarbamylase Deficiency

The RAC will meet December 8-10 to discuss the biology of adenoviral vectors and adverse events, the ornithine transcarbamylase (OTC) deficiency trial and the death in the trial, and disclosure of adverse events. FDA will have a nonvoting representative as usual, and will be a part of the working group that will report on the adverse events reported by more than 70 investigators using adenoviral vectors.

Background: The RAC discussed the phase 1 protocol for Adenovirus vector Expressing the OTC Gene in December, 1995, approximately 6 months before Dr. Wilson submitted the IND to CBER. The protocol that was discussed at the RAC involved vector administration via intrahepatic artery (IHA). Much of the discussion involved the route of administration: Dr. Erickson questioned the choice of IHA because it was invasive and impractical as a means for chronic administration (and questioned the feasibility of chronic administration in general because of immune responses). Dr. Erickson also was concerned that patients who received vector via the IHA could develop an inflammatory response, as was seen in the baboon experiments. This might put patients with partial deletions of the gene into a crisis since the liver was their only source for OTC.

The investigators responded that they chose the IHA route because it was potentially safer in that it would limit exposure to only a portion of the liver, while the intravenous (IV) route targeted the entire liver. They also stated that, if single dose administration was safe and indicated gene expression, a potential niche for this product could be single administration for patients in impending crisis. However, they also planned to move into a multiple administration protocol if warranted following the single dose study.

The RAC ultimately recommended approval of the study with the proviso that the route be changed to IV. The investigators (Drs. Wilson and Batshaw) agreed to the change.

The investigators came to CBER for a pre-IND meeting in early 1996, and at that time proposed that the route of administration would be IV. Animal data in a murine model of OTC deficiency showed that this approach was feasible in achieving gene correction, however, only limited safety data were available for the IV route of injection. Additionally, CBER raised the concern that the IV route had the potential for systemic dissemination of vector signal to non-target organs including the gonads, and that no studies had been conducted to address this risk. The investigators agreed to conduct further safety and biodistribution studies prior to submission of the IND.

The initial protocol submitted to CBER in May 1996 involved a single IV dose of vector, to patients with partial OTC deficiency or who were mothers of previously affected offspring (hemizygous for the OTC gene). During the protocol review, CBER carefully considered the RAC discussions in their decision process. When the investigators presented to the RAC, no preclinical information on vector dissemination to other (non-target) tissues was available. However, CBER's review of the biodistribution data included in the original IND submission determined that significant and persistent dissemination to gonadal tissues was occurring following IV administration of the vector, and that at 90 days after vector injection the level of signal in the gonads was approximately equal to that in the target organ (liver). At that time and up until very recently, the potential for vector dissemination outside the target organ, and particularly to gonadal tissue was considered an unacceptable risk. The agency ultimately determined that the study could not begin and placed it on clinical hold for safety issues regarding the gonadal dissemination. The investigators were requested as part of the clinical hold letter to provide data demonstrating whether vector was detectable in germ cells, and to explore whether the more targeted IHA route of administration would lessen the risk of gonadal distribution as compared to the IV injection.

To address the clinical hold, the sponsor conducted a cross-breeding mating study in mice treated with or without the OTC vector, and again showed vector dissemination to gonadal

tissues (both ovaries and testes) following IV injection route. In contrast, data following IHA administration to baboons indicated minimal inflammatory response in the liver and no dissemination to ovaries or other non-target tissue, at doses approximating those proposed for the clinical trial.

Based on the animal data, the agency determined that the IHA route was safer, in terms of decreasing the risk of dissemination of vector to gonadal tissues and potential germ-line transmission of the foreign gene. The clinical hold was lifted following agreement by the investigators and CBER to protocol modifications that included the change in route of administration, as well as other modifications to enhance patient safety.

Future Considerations:

The future will bring exponential complexity to our goal of improving and promoting the public health. For example, sponsors are already beginning to discuss the possibility of using human nonreplicating lentiviral vectors derived from HIV from AIDS patients. The apparent success in inducing peripheral and cardiac vascularization by both viral and plasmid vectors has led to several sponsors having late phase II and early phase III trials for the potentially huge area of cardiovascular disease. FDA will be formulating new Chemistry and Manufacturing Controls requirements, as well as appropriate clinical end points for these trials.

FDA cannot regulate nor directly oversee all the innovative work being carried out in academic institutions, yet it is clear that many exciting innovations emerge from academia. A means is needed whereby the FDA can enlarge its oversight when it is appropriate and timely. The success of the 1996 and 1997 Gene Therapy workshops demonstrates that FDA can proactively educate sponsors in requirements, thus reducing development costs and time. We anticipate that the publication of the proposed rule on Good Tissue Practices (GTPs, under the Tissue Action Plan) will greatly enhance these efforts, as the GTPs are intended to serve as the basis for cell and gene therapy facilities, as well as for tissue banks.

Several regulatory issues will be addressed in the near future. A regulatory approach will be implemented which will allow the approval of reagents necessary to prepare gene therapy products, but which in themselves are not expected to effect a clinical benefit to the patient. An updated and revised Draft Guidance Document for Cellular and Gene Therapies was issued in 1998, and was updated in 1999 with new FDA requirements for safety testing of murine retroviral vectors that significantly reduce sponsor burden, while maintaining patient safety. The advantages of public discussion of proposed and ongoing INDs through the RAC public oversight process have led to development of a proposed disclosure rule for gene therapy and xenotransplantation protocols that would allow continued public discussion of novel protocols and products.

The FDA and NIH have formed a Rare Diseases Initiative to coordinate efforts to foster development of gene therapeutics intended to treat genetic diseases affecting small populations. The Initiative's primary objective is to develop a shared portfolio of non-proprietary pre-

clinical safety data for viral vectors that can be used to support the safety evaluation of gene therapeutics. Its main goals are to (1) design and perform pre-clinical toxicological testing to evaluate vector-specific toxicities; (2) provide a mechanism for cooperative data sharing among NIH-sponsored as well as commercial investigators; (3) develop new biostatistical models for efficacy evaluation in small patient populations; and (4) encourage innovative approaches to small scale drug development.

TAB A

Federal Register

**Thursday
October 14, 1993**

Part II

Department of Health and Human Services

Food and Drug Administration

**Application of Current Statutory
Authorities to Human Somatic Cell
Therapy Products and Gene Therapy
Products; Notice**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93N-0173]

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is making available, through this document, a statement of the manner in which FDA's current statutory authorities governing therapeutic products apply to human somatic cell therapy products and gene therapy products. FDA is publishing this statement in response to requests that the agency clarify its regulatory approach and provide guidance to manufacturers of products intended to be used in somatic cell therapy or gene therapy. As scientific knowledge in the area of somatic cell and gene therapy continues to accumulate and evolve, the agency's approach may also evolve.

DATES: Submit written comments on the document by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Submit investigational new drug applications (IND's) for somatic cell therapy and gene therapy products to the Division of Application Review and Policy (HFM-585), Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Submit written requests for single copies of the document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" to the Congressional and Consumer Affairs Branch (HFM-12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-295-9000. Send two self-addressed adhesive labels to assist that office in processing requests.

FOR FURTHER INFORMATION CONTACT: Ann Reed Gaines, Center for Biologics Evaluation and Research (HFM-635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

As a consequence of scientific and biotechnological progress during the past decade, new therapies involving somatic cells and genetic material are being investigated, and commercial development of products for use in somatic cell therapies and gene therapies is occurring. Existing FDA statutory authorities, although enacted prior to the advent of somatic cell and gene therapies, are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing. Manufacturers and other interested parties have questioned FDA regarding how such products will be regulated. This statement outlines the current regulatory approach to products intended for use in somatic cell and gene therapies.

II. Background

A. Legal Authorities

FDA regulates numerous kinds of products intended to prevent, treat, or diagnose diseases or injuries under legal authorities established in the Public Health Service Act (the PHS Act) and the Federal Food, Drug, and Cosmetic Act (the act). Section 351(a) of the PHS Act (42 U.S.C. 262(a)) identifies a biological product as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." Section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) defines the term "drug," in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." The term "device" is defined in section 201(h) of the act, in part, as:

*** "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article *** intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, *** which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Both the "drug" definition and the "device" definition also include articles "intended to affect the structure or any function of the body."

Section 351(a) of the PHS Act requires premarket approval for biological

products. Licenses are to be issued upon a showing that the establishments and products "meet standards, designed to insure the continued safety, purity, and potency of such products * * *" (42 U.S.C. 262(d)). A biological product's effectiveness for its intended uses must be shown as part of the statutory requirement for potency (21 CFR 600.3(s)). At the investigational stages, when the products are being studied in clinical trials to gather safety and effectiveness data, biological products must meet the requirements of part 312 (21 CFR part 312). FDA's biologics regulations require the submission of both product license applications (PLA's) and establishment license applications (ELA's) (21 CFR 601.1 through 601.10). Biologics establishments and products must satisfy detailed standards set forth in the regulations (21 CFR parts 600 through 680).

Section 351(b) of the PHS Act prohibits falsely labeling or marking a biological product. Under section 361 of the PHS Act (42 U.S.C. 264), the agency may promulgate regulations to prevent the introduction, transmission, or spread of communicable diseases.

Products considered to be biological products subject to the provisions of section 351 of the PHS Act are simultaneously also drugs or devices subject to the applicable provisions under the act. For example, the adulteration, misbranding, and registration provisions of the act would apply to the product as a drug or device.

Under section 501 of the act (21 U.S.C. 351), both drugs and devices are considered adulterated for any of a number of specified reasons. Included among these adulteration provisions is the requirement that the methods and facilities and controls used for manufacture, processing, packing, and holding or installation conform with current good manufacturing practice (CGMP) regulations (21 U.S.C. 351(a)(2)(B) and (h)). FDA's implementing regulations codified at 21 CFR parts 211 and 820 specify the drug and device CGMP requirements.

Section 502 of the act (21 U.S.C. 352) sets forth misbranding provisions that apply to drugs and devices. Among other circumstances, a drug or device is considered misbranded if the labeling is false or misleading or if the labeling fails to bear adequate directions for use or adequate warnings against unsafe use (21 U.S.C. 352(a) and (f)). Any drug or device is also misbranded if it is dangerous to health when used in the manner or with the frequency suggested in the labeling (21 U.S.C. 352(j)). For prescription drugs and restricted

devices, section 502 of the act describes certain information that must be included in all advertisements or other printed material (21 U.S.C. 352(n) and (r)). FDA's regulations also establish labeling and advertising requirements in more detail (21 CFR parts 201, 202, and 801).

Section 510 of the act (21 U.S.C. 360) requires persons who own or operate establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices (with certain exceptions) to register those establishments with FDA. Individuals who must register their establishments under section 510 of the act must also file a list of all the drugs and devices being made or processed at the establishment. FDA's registration regulations are codified at 21 CFR parts 207 and 807.

Although products regulated by FDA as biological products must also meet drug or device requirements, the agency does not require duplicate premarket approvals. For example, if FDA requires a PLA to be submitted for the product as a biologic, the agency does not also require submission of a new drug application (NDA) or a device premarket approval application (PMA).

The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biologics and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the act (21 U.S.C. 352(f)(1); 21 CFR 201.5, 201.100(c)(2)). Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)). The act contains a presumption of interstate commerce for devices (section 709 of the act (21 U.S.C. 379a)).

Both the PHS Act and the act provide authority for enforcement of the various statutory requirements. FDA is authorized to conduct inspections to determine compliance with regulatory requirements (42 U.S.C. 262(c) and 21

U.S.C. 360(h) and 374). Approved PMA's may be suspended or revoked (42 U.S.C. 262(a) and 21 U.S.C. 355(e) and 360(e)). Biological products and devices may be recalled under certain circumstances (42 U.S.C. 262(d)(2) and 21 U.S.C. 360(h)). Judicial actions, including seizures, injunctions, and criminal prosecutions, may also be initiated (42 U.S.C. 262(f) and 21 U.S.C. 332, 333, and 334).

Some products may contain a combination of biological products and drugs or devices. Under a provision of the Safe Medical Devices Act of 1990, FDA determines the primary mode of action of the combination products (21 U.S.C. 353(g)), then assigns the primary jurisdiction for review of the product within the agency based on that determination. FDA has established procedures for designating the organization within FDA (i.e., the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH)) to review combination products or any other products where the agency center with primary jurisdiction is unclear (21 CFR 3.1 through 3.10). CBER, CDER, and CDRH have also entered into intercenter agreements to clarify the centers' responsibilities for reviewing various kinds of products.

B. Regulation of Somatic Cell and Gene Therapy Products

This statement is intended to present the agency's current approach to regulating somatic cell and gene therapy products. For the purpose of this statement, somatic cell therapy products are defined as autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. Cellular products intended for use as somatic cell therapy are biological products subject to regulation pursuant to the PHS Act (42 U.S.C. 262) and also fall within the definition of drugs in the act (21 U.S.C. 321(g)). As biological products, somatic cell therapy products are subject to establishment and product licensure to ensure product safety, purity, and potency. At the investigational stage, these products must be in compliance with part 312. Clinical trials are, therefore, to be conducted under IND's. As drugs, somatic cell therapy products are also

subject to drug requirements such as conformity with CGMP regulations.

FDA has not required premarketing approval for many types of transplantation, including bone marrow transplants. However, recent scientific and biotechnological developments now enable bone marrow to be manufactured into a somatic cell therapy product. Such products are subject to FDA regulation consistent with the approach to other somatic cell therapies described in this statement. In addition, other forms of transplantation, such as the transfer of whole organs and tissues, have been, or are currently being reassessed and addressed by FDA or other Federal agencies in light of current knowledge and technological advances.

Gene therapy products are defined for the purpose of this statement as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products (e.g., those containing viral vectors) to be administered to humans fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act. Other gene therapy products, such as chemically synthesized products, meet the drug definition but not the biological product definition and are regulated under the relevant provisions of the act only.

Biological products intended for use as source materials for further manufacture into licensed somatic cell therapy products or gene therapy products require premarketing approval as biological products intended for further manufacture when they are shipped from one legal entity to another. Such products would be considered part of a shared manufacturing arrangement in which: (1) Two or more manufacturers perform different aspects of the manufacture of a product, (2) neither performs nor is licensed to perform all aspects of the manufacture, and (3) each manufacturer holds product and establishment license applications. In a shared manufacturing arrangement, FDA accepts only license applications for biological products intended for further manufacture that specify the licensed manufacturer or manufacturers to which the intermediate product will be shipped and approves such applications only after demonstration of safety and efficacy of the end product. For example, biological gene therapy products intended for use *ex vivo* in the manufacture of genetically altered cells for somatic cell therapies will require premarketing approval as biological

products intended for further manufacture when shipped from one legal entity to another and will be approved only when the final somatic cell therapy product is approved. For further discussion regarding shared manufacturing, refer to FDA's policy statement concerning cooperative manufacturing arrangements for licensed biological products, which was published in the *Federal Register* on November 25, 1992 (57 FR 55544).

In accordance with the statutory provisions governing biological products and drugs, a somatic cell therapy product or gene therapy product must be the subject of an IND in compliance with part 312 or of an approved PLA regardless of whether the finished product is shipped across State lines.

The manufacture of somatic cell therapy products or gene therapy products will involve many ancillary products used as part of the manufacturing process. The ancillary products are not intended to be present in final products but may have an impact on the safety, purity, or potency of the products under manufacture. Such ancillary products meet the definition of devices and, if marketed, will be regulated under the act device authorities, with the appropriate type of regulatory control being determined according to codified procedures (e.g., investigational device exemption (IDE)—21 CFR part 812; premarket approval (PMA)—21 CFR part 814; premarket notification (510(k))—21 CFR 870.81 through 807.97). When these ancillary products are used in the manufacturing of somatic cell or gene therapy products, they become subject to drug CGMP's, in particular for components and containers (21 CFR 211.80 through 211.94 and 211.101(b) and (c)).

Some of the ancillary products will already be marketed as medical devices, drugs, or biological products. When an ancillary product used as a component of the manufacturing process is marketed but not labeled for the specific use, such use may initially be described under the IND for the final somatic cell or gene therapy product. Such use of ancillary products by manufacturers of investigational somatic cell therapy or gene therapy products is contingent upon the submission of complete descriptions of the use of the ancillary product in the manufacturing process.

If the ancillary product used as a component of the manufacturing process does not have marketing approval, manufacturers of the somatic cell or gene therapy product must submit or provide cross-reference to a

complete description of the manufacturing process, specifications, qualification, and acceptance criteria of the ancillary product. This information may be filed by the sponsor of the IND for the somatic cell or gene therapy product, may be filed in an IND or IDE by the manufacturer of an ancillary product, or may be made available by the manufacturer of the ancillary product in a master file format, as defined in 21 CFR 814.3(d) and discussed in 21 CFR 814.20(c).

Manufacturers who wish to market ancillary products for use in the manufacturing of somatic cell or gene therapy products must file either: (1) A 510(k), (2) a PMA, (3) an amendment to an existing 510(k), PMA, NDA, or PLA.

The manufacture of somatic cell therapy products or gene therapy products may involve components of manufacture intentionally present as part of the final products. Products containing both a somatic cell component and another drug or device component in the final product will be handled as combination products.

The following statement succinctly describes FDA's current approach to regulating somatic cell therapy and gene therapy products with primary emphasis on premarket approval issues. As previously discussed, products that meet the biologic, drug, or device definition must also comply with other relevant provisions of the PHS Act and the act. Manufacturers may also find useful information in FDA's document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," Docket No. 91N-0428, available from CBER's Congressional and Consumer Affairs Branch (address above).

III. Statement

A. Somatic Cell Therapy

1. Definition

Somatic cell therapy is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics.

2. Cells Subject To Licensure as Final Products When Intended for Use as Somatic Cell Therapy

Cells subject to licensure as final biological products when intended for use as somatic cell therapy include cells

manipulated in a way that changes the biological characteristics of the cell population (e.g., by expansion, selection, encapsulation, activation, or genetic modification as a part of gene therapy as defined in section III.B.1. of this document).

Examples include the following: (1) Autologous or allogeneic lymphocytes activated and expanded ex vivo (e.g., lymphokine-activated killer cells (LAK), tumor infiltrating lymphocytes (TIL cells), antigen specific clones); (2) encapsulated autologous, allogeneic, or xenogeneic cells or cultured cell lines intended to secrete a bioactive factor or factors (e.g., insulin, growth hormone, a neurotransmitter); (3) autologous or allogeneic somatic cells (e.g., hepatocytes, myocytes, fibroblasts, bone marrow- or blood-derived hematopoietic stem cells, lymphocytes) that have been genetically modified; (4) cultured cell lines; and (5) autologous or allogeneic bone marrow transplants using expanded or activated bone marrow cells. (For bone marrow products whose status is not clear, consult CBER.)

3. Cells and Tissues Subject to Licensure as Source Material

Cells and tissues subject to biological product licensure as source material include allogeneic or xenogeneic cells harvested by other than the final product license holder and intended for manufacture into a somatic cell product. Examples include the following: (1) Muscle cells removed from donors and shipped to a manufacturer for expansion into a muscle cell therapy, (2) animal cells harvested at an animal care facility and shipped to a manufacturer for encapsulation or other manufacturing steps into a somatic cell therapy, and (3) other human tissue harvested from donors and shipped to another legal entity for manufacture into a somatic cell therapy.

4. Cells for Which Applications for Approval Prior to Marketing are not Presently Required

Cells for which applications for approval prior to marketing are not required at the present time include the following: (1) Cell transplants not having the characteristics described in sections III.A.2. and III.A.3. of this document, and (2) minimally manipulated or purged bone marrow transplants. Examples include the following: (1) Allogeneic bone marrow transplantation employing ex vivo T cell purging with a monoclonal antibody approved for such purging, (2) autologous bone marrow transplantation employing ex vivo tumor cell purging by an approved agent, and (3)

autologous bone marrow transplantation employing bone marrow enriched for stem cells by immunoadherence. (However, extensive manipulation of bone marrow for the purpose of obtaining purified stem cell populations would result in a somatic cell therapy subject to licensure.)

B. Gene Therapy

1. Definition

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.

2. Final Products Containing the Genetic Material Intended for Gene Therapy

Final products containing the genetic material intended for gene therapy are regulated as biological products requiring PLA's (e.g., viral vectors containing genetic material to be transferred, *ex vivo* transduced cells and analogous products) or as drugs requiring NDA's (e.g., synthetic products) regardless of whether they are intended for use *in vivo* or *ex vivo*. Gene therapy products that are licensed biological products will be approved as biological products intended for further manufacture if they are intended to be used *ex vivo* during the manufacture of genetically altered cells.

Examples include the following: (1) A synthetic polynucleotide sequence intended to alter a specific genetic sequence in human somatic cells after systemic administration is regulated as a drug requiring an NDA; (2) a retroviral vector containing the adenosine deaminase (ADA) gene, intended to be administered intravenously to the patient, is regulated as a biological product requiring a PLA; and (3) a

retroviral vector containing the ADA gene and intended to modify cells *ex vivo* is regulated as a biological product intended for further manufacture requiring a PLA.

3. Viral Vector Systems Intended for Further Manufacture Into Final Products

The manufacture and quality control of viral vector systems (i.e., not containing the complete genetic material) that are designed to serve as the starting point for further manufacture into final products (i.e., insertion of additional genetic material into the vector) may be described in a drug master file.

C. Ancillary Products Used during Production of Somatic Cell Therapies

Numerous products will be used during production of somatic cell therapy. Examples include the following: (1) Bioreactors and cell culturing systems, (2) components of culture media, (3) drug- or biologic-like components used to activate or otherwise change the biological characteristics of the cells, (4) certain antisense polynucleotides, and (5) agents used to purge or select or stimulate specific cell populations. A common characteristic of these products is that they are intended to act on the cells, rather than to have an independent effect on the patient. Additionally, the intended action of these products is not dependent upon incorporation into the somatic cell with maintenance of the products' structural or functional integrity.

These products meet the definition of medical devices. They are regulated as devices, with the type of regulatory control being determined according to codified procedures. In contrast, products administered directly to patients or products whose function requires incorporation into the somatic cells with maintenance to some degree of structural or functional integrity (e.g., viral or other vectors containing genetic material to be used in gene therapy) are not considered ancillary products; rather, they are regulated as drugs or biological products.

The center primarily responsible for regulating a particular device will be designated according to the current intercenter agreements. For example, according to the current agreement, CDER will regulate the synthetic antisense compounds, CBER will be responsible for monoclonal antibody-based purging agents, and CDRH will oversee the approval of bioreactors.

D. Combination Products

Many somatic cell products administered to patients will be combinations of a biological product and a device or of a drug, a biological product, and a device. Examples include the following: (1) Encapsulated pancreatic islet cells secreting insulin, and (2) a device containing encapsulated cells secreting a neurotransmitter. The combination products for which the primary mechanism of action is that of the somatic cell therapy component will be regulated as biological products.

IV. Comments

FDA recognizes that somatic cell and gene therapy products constitute a new and emerging scientific area. The agency will review and consider written comments on the regulatory approach set forth in this notice. Any comments received will be considered in determining whether amendments to, or revisions of, the approach are warranted. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments received are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 24, 1993.

Michael R. Taylor,

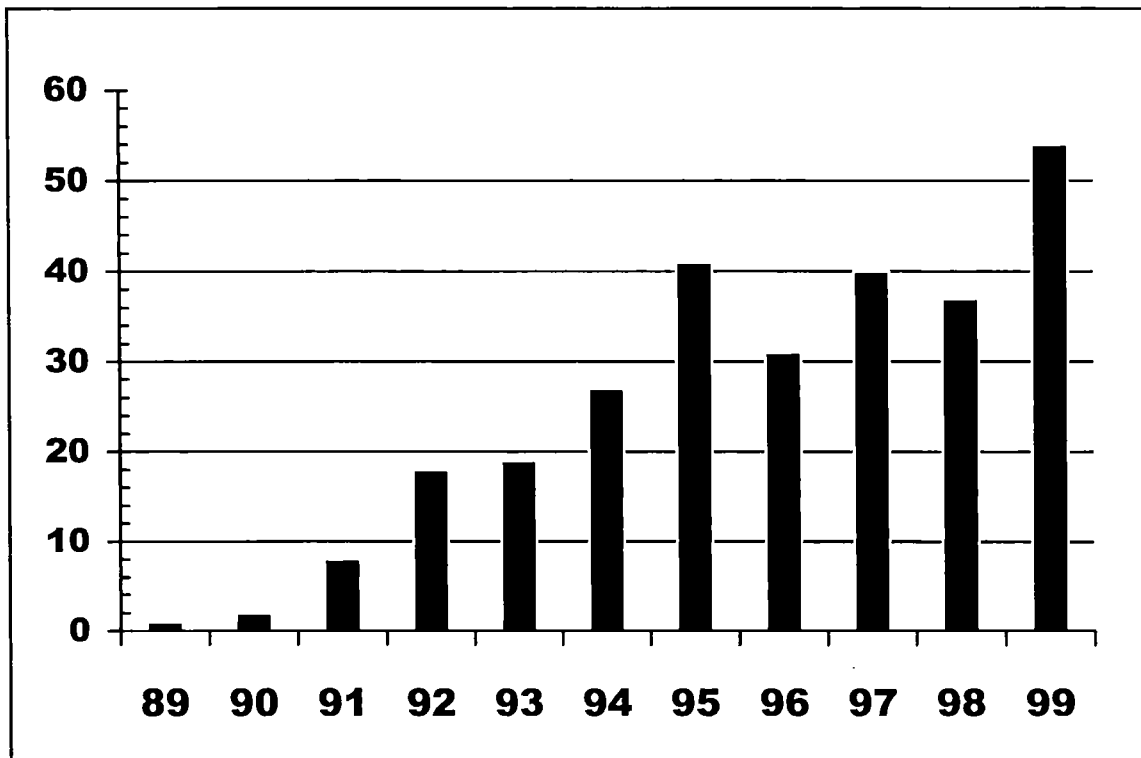
Deputy Commissioner for Policy.

[FR Doc. 93-24938 Filed 10-13-93; 8:45 am]

BILLING CODE 4160-01-F

TAB B

NEW GENE THERAPY INDS PER YEAR



TAB C

November 23, 1999

History of RAC-FDA Interactions

Regulation of biological products transferred from the NIH (Division Biologics Standards) to the Food and Drug Administration (Bureau of Biologics)

1975 Asilomar meeting. Scientists voluntarily call for halt to recombinant DNA research. Recombinant DNA Advisory Committee formed to write Guidelines for research, incorporated within the NIH

1976-1986 Many reviews of research proposals ceded to other agencies; biotech products for human use began to be approved in early 1980s by FDA

1984 First Federal Register (FR) proposal for coordinated oversight of biotechnology. FDA proposed that gene therapies would be regulated as biologics, while the NIH RAC would consider reviews of NIH funded studies, and commercial studies on a voluntary basis.

1986 Reproposed coordinated framework further delineated responsibilities of responsible agencies. FDA formally declared in a policy statement that gene therapies would be regulated as biologics. Of note, for approval of commercial gene therapy products, FDA has sole responsibility, while for gene therapy research jurisdiction, the FDA and the NIH RAC share oversight, with FDA as the lead agency. In the latter case, this responsibility means that the approval of experiments in humans is vested with the FDA.

1986 Establishment of Gene Therapy Subcommittee of the RAC

1988 First RAC approval of a gene transfer experiment in humans, beginning of dual oversight of gene therapies; First FDA authorization of a gene therapy experiment

1991 Publication of FDA Points to Consider for gene therapies

1993 Formation of FDA Division of Cellular and Gene Therapies; Publication of Federal Register Notice of FDA authorities to regulate cellular and gene therapies

1994 Joint statement by Dr. Kessler and Dr. Varmus at National Task Force on AIDS Drug Development meeting to streamline and consolidate reviews of gene therapy protocols; NIH and FDA participate in House hearing on gene therapies, and explain consolidated review

1995 Publication of consolidated review process in FR Ad hoc committee chaired by Inder Verma suggests that RAC acknowledge case by case review to FDA, hold public in depth discussions on newer issues such as novel vectors, in utero gene therapy, and maintain a public database of gene therapy protocols

1996 RAC meets only once in 1996 (December). NIH proposes to implement changes of Verma committee.

1997 NIH amends guidelines to acknowledge sole approval authority vested in FDA, augments guidelines to include Gene Therapy Policy Conferences

1998 NIH/FDA Gene Therapy Policy Conference on Lentiviral Vectors

1999 NIH/FDA Gene Therapy Policy Conference on In Utero Gene Therapy; FDA/RAC discussion on gonadal distribution of vectors; FDA/RAC discussion on adenoviral gene therapy vectors, death in gene therapy study, harmonization of adverse event reporting requirements

TAB D

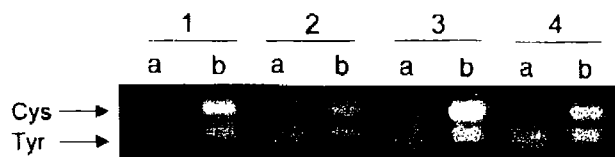


Fig. 2 *RsaI* digest of amplified genomic DNA from four 5474A/5569A compound heterozygotes. PCR reactions are shown using the intron 3 sense primer and the intron 4 antisense primer that included the 5569G/A polymorphism site⁴ ('a'), and the intron 3 sense primer and the alternative intron 4 antisense primer that avoided the 5569G/A polymorphism site ('b'). PCR product 'a' is 387 bp and 'b' is 393 bp. Normal DNA *RsaI* cleavage of product 'a' produces 247-bp and 140-bp fragments, and cleavage of product 'b', 247-bp and 146-bp fragments. The presence of the 5474A (C282Y) mutation results in cleavage of the 140-bp fragment ('a') into 111-bp and 29-bp fragments and cleavage of the 146-bp fragment ('b') into 117 bp and 29 bp. *RsaI* digestion of reaction 'a' produced a single fragment of 111 bp (Tyr) that incorrectly indicated a 5474A/5474A homozygote. In contrast, *RsaI* digestion of reaction 'b' produced fragments of 146 bp (Cys) and 117 bp (Tyr), correctly identifying 5474A heterozygotes. DNA from two 5569A homozygotes initially did not amplify with the original Feder *et al.* primers, but were later identified by repeat PCR using the new primer assay. We performed other experiments using the Feder *et al.* primers at annealing temperatures of 62 °C, 60 °C, 58 °C and 56 °C with DNA from five 5474A/5569A compound heterozygotes. We correctly identified only one of these as heterozygous for 5474A by the *RsaI* assay at an annealing temperature of 60 °C or less. This suggests that further modifications of assay conditions may reduce the possibility of false-positive genetic testing in the presence of the 5569A polymorphism.

hood estimate of linkage disequilibrium *D* (ref. 5) was 0.71 ($P < 0.005$), confirming the presence of moderate to strong linkage disequilibrium between the 2 variant sites. It is unlikely that the 5569A polymorphism has functional significance, because it is found within intron 4 and does not disrupt a splice-site consensus sequence. Moreover, all 5474A/5569A compound heterozygotes had a transferrin saturation in the normal

range (mean 31%, range 20–40%). In our population study, the prevalence of haemochromatosis was reduced from 1 in 168 to 1 in 327 by the use of the new primers. These results have major public health implications regarding the use of population screening for haemochromatosis^{6,7}. Individuals previously considered to be non-expressing 5474A homozygotes on the basis of a PCR-based restriction

endonuclease digestion assay using the original Feder *et al.* primers require confirmatory testing.

Acknowledgements

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FDA comments on phase I clinical trials without vector biodistribution data

In the June issue of *Nature Genetics*, Haig Kazazian discussed calculations presented at a Recombinant DNA Advisory Committee (RAC) meeting held on 12 March 1999 on inadvertent germline alteration¹. He mentioned a proposed safety limit on genetic insertions, which was attributed to the Food and Drug Administration (FDA). We would like to clarify the FDA's policy. Rather than a specific limit, policy decisions about risks of genetic insertion are based on disease severity, age, life expectancy and reproductive status, as well as vector biology and animal safety data.

The FDA agrees with Kazazian that the natural rate of insertional mutations should be considered when developing regulations, and his presentation at the meeting was a key factor enabling a decision on policy to be reached. There are also other relevant factors to consider. Public reaction to a harmful germline mutation caused, even inadvertently, by gene therapy might differ from reaction to insertional mutations in nature. In addition, expression of therapeutic genes in inappropriate tissues or

stages of development may have harmful consequences.

Germline alterations are a theoretical risk of somatic cell gene therapy that extends beyond consenting patients to unborn generations. Germline gene therapy² does not presently have societal endorsement^{3,4}. Previously, when cells were transduced by gene therapy vectors outside the body and used to treat serious diseases, inadvertent germline effects were not considered a significant risk. With direct administration of gene therapy vectors to patients, however, potential distribution to unintended tissues raises concern about effects on sperm or ova genomes. Concern is also heightened by extension of gene therapy to patients with milder conditions and greater reproductive potential.

The FDA determined that public discussion of inadvertent germline alteration was necessary to reach a consensus on policy. At the RAC meeting held in March, the FDA reviewed vector biodistribution data from pre-clinical studies, including unexpectedly persistent PCR signals in gonads

<http://www.nih.gov/od/orda/3-99sum.htm>). RAC and public representatives concluded that a low risk of germline alteration was acceptable for some phase I trials. While PCR signals in gonads do not demonstrate that vector is in germ cells, further studies were recommended in such cases. Based on this public discussion, the FDA now allows certain therapies to enter initial clinical trials despite incomplete biodistribution data or detection of gonadal presence of the vector. Investigators are required, however, to address vector biodistribution and potential germline transmission during product development before licensure.

Acknowledgements

We thank E. Max, J. Kassiss and J. Siegel for helpful comments.

Suzanne Epstein, Steven Bauer, Andra Miller, Anne Pilaro & Philip Noguchi
Division of Cellular and Gene Therapies, CBER, FDA, 1401 Rockville Pike, HFM-521, Rockville, Maryland 20852-1448, USA.

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TAB E



November 5, 1999

Dear Gene Therapy IND Sponsor/Principal Investigator:

As you are aware, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have been working together to optimize and streamline federal regulation and oversight of human gene transfer research. FDA and NIH each make unique and complementary contributions to the scientific evaluation of safety and potential efficacy of human gene therapy trials. FDA has statutory authority to permit an Investigational New Drug (IND) to go into effect or, if necessary, to place an IND on clinical hold, in order to ensure the safety of human subjects. The NIH is responsible for convening the Recombinant DNA Advisory Committee (RAC) which conducts public scientific and ethical review and discussion of novel applications of human gene transfer, as well as important public policy issues.

This letter outlines an established process for submission of a gene therapy IND and any subsequent adverse event reports to the Center for Biologics Evaluation and Research (CBER), FDA, and how that process relates to the submission of gene therapy protocols and adverse event reports to the NIH Office of Recombinant DNA Activities (ORDA), as required by the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. The submission process was initially established in 1994 through a cooperative effort between FDA and NIH.

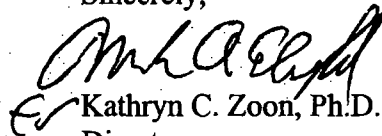
- The documentation required in Appendix M-I of the current *NIH Guidelines* (<http://www.nih.gov/od/orda/toc.htm>) should be submitted to NIH/ORDA prior to the submission of an IND to FDA. This will help to ensure that novel issues will be identified and discussed publicly in a timely manner.
- FDA will notify NIH/ORDA of the receipt of a gene therapy IND to assist NIH/ORDA in monitoring investigator compliance with the *NIH Guidelines*.
- In accordance with the FDA regulations found at US Code of Federal Regulations, Title 21, part 312.32 "IND Safety Reports" and *NIH Guidelines, Appendix M-VII-C "Adverse Event Reporting,"* investigators/sponsors are expected to report all serious adverse events to both the FDA and NIH.
- FDA will notify NIH/ORDA of the receipt of an adverse event report on a gene therapy IND to enhance investigator compliance with the *NIH Guidelines*.
- Within 15 working days after receipt by NIH/ORDA of a complete submission, the RAC will determine whether a protocol is novel and, therefore, requires public RAC review.

NIH/ORDA will notify FDA within one working day of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. The FDA will request that the sponsor delay initiation of, or suspend an ongoing protocol until the RAC has determined whether the protocol requires public review.

If the RAC decides that full public review is warranted, the FDA will request, at the completion of its IND review (within 30 days of receipt of the IND or when the IND is allowed to proceed by FDA), that sponsors delay initiation of the protocol until after completion of the RAC review process.

These policies and procedures will enable investigators and sponsors to initiate important research in a timely fashion under FDA regulations and, at the same time, ensure that novel gene transfer experiments benefit from full public review by the RAC.

Sincerely,

A handwritten signature in dark ink, appearing to read 'Kathryn C. Zoon', is written over the printed name.

Kathryn C. Zoon, Ph.D.

Director

Center for Biologics Evaluation and
Research

TAB F

DEPARTMENT OF HEALTH AND HUMAN SERVICES**National Institutes of Health****Office of Recombinant DNA Activities;
Recombinant DNA Research:
Proposed Actions Under the NIH
Guidelines**

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

SUMMARY: The purpose of this document is to inform the public of proposed changes to the NIH Guidelines related to the reporting of serious adverse events involving human gene transfer research. This notice describes a proposed action to amend the NIH Guidelines regarding the reporting and public disclosure of serious adverse events.

DATES: The public is encouraged to submit written comments on these proposed changes to the NIH Office of Recombinant DNA Activities (ORDA). Written comments may be submitted to NIH/ORDA in paper or electronic form. Written comments received by December 3, 1999, will be reproduced and distributed to the RAC for consideration at its December 8–10, 1999, meeting.

All comments received in response to this notice will be considered by the NIH and will be available for public inspection in the NIH/ORDA office weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional information about these proposed changes to the NIH Guidelines, please contact the Office of Recombinant DNA Activities (ORDA) by e-mail at: ci4e@nih.gov, or telephone at: 301–496–9838. Written comments on these proposed changes to the NIH Guidelines can be submitted by e-mail to: ci4e@nih.gov, fax to: 301–496–9839, or mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010.

For additional information about the December 8–10, 1999, RAC meeting at which these proposed changes will be deliberated, please visit the NIH/ORDA web site at: <http://www.nih.gov/od/ora/>.

SUPPLEMENTARY INFORMATION: Appendix M–VII–C of the NIH Guidelines requires Principal Investigators (or their designated sponsors) to report serious

adverse events immediately to the local Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), Office for Protection from Research Risks (OPRR) (if applicable), NIH/ORDA, and Food and Drug Administration (FDA).

All non-NIH funded projects involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH support for projects involving such techniques must comply with the NIH Guidelines. Noncompliance may result in: (i) Suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

All gene transfer clinical studies are subject to FDA regulations found in volume 21 of the Code of Federal Regulations (CFR), including specific requirements at 21 CFR 312.32 related to adverse events.

The immediate reporting of serious adverse events to NIH/ORDA by investigators allows rapid notification of the RAC. This, in turn, allows notification, as appropriate, of other IBCs, IRBs, and Principal Investigators in the field. Immediate reporting also provides a unique mechanism for early recognition of trends in the occurrence of serious adverse events that may raise significant implications for the safety of patients enrolled in similar human gene transfer studies. For example, there have been several instances in which public RAC discussion of serious adverse events has resulted in important changes in the design of vectors for gene delivery. When deemed appropriate, NIH/ORDA will initiate additional data collection for a comprehensive and public review by the RAC and ad hoc experts. This process fosters broad public awareness of issues and developments in human gene transfer research. The comprehensive public review of data by the RAC is a critical component of Federal oversight of gene transfer research.

Recently some investigators and sponsors have begun to designate human gene transfer protocols or serious adverse event reports confidential, thereby precluding public RAC review. Out of concern about this development, the NIH requested that the RAC consider whether the requirement for serious adverse event reporting as set forth in the NIH Guidelines needed to be clarified.

During the September 2–3, 1999, meeting, the RAC developed the following consensus statement with regard to serious adverse event reporting

to NIH/ORDA and the RAC: "Adverse event reports shall not be designated as confidential, either in whole or in part. Adverse event reports are essential to decision-making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports must be made available for public discussion [by the RAC] without the inclusion of proprietary or trade secret information."

Some investigators have not complied with the NIH Guidelines requirement to report serious adverse events immediately to the NIH/ORDA. While the NIH Guidelines are clear on this matter, the NIH is proposing to amend the NIH Guidelines to restate the requirements for serious adverse event reporting and to include: (1) A definition of serious adverse events and a stipulation of the time-frame in which they are to be reported in writing (adapted from 21 CFR 312.32 IND Safety Reports); (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 Appendix M–VII–C will be considered public unless NIH ORDA determines that there are exceptional circumstances; and (3) a directive that serious adverse event reports submitted to ORDA be stripped of individually-identifiable patient information.

Proposed Amendments to the NIH Guidelines

A new Section I–E–7 is added to read:

"Section I–E–7. A "serious adverse event" is defined as any expected or unexpected adverse event, related or unrelated to the intervention, occurring at any dose that results in any of the following outcomes; death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

Appendix M, Points To Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into One or More Human Subjects (Points To Consider)

Appendix M-VII-C, Serious Adverse Events, is proposed to read:

"Appendix M-VII-C-1, Serious Adverse Event Reporting

"Principal Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report immediately in writing any serious adverse event (as defined in Section I-E-7) to the local Institutional Review Board, Institutional Biosafety Committee, Office for Protection from Research Risks (if applicable), NIH/ORDA, and FDA.

"Serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential as defined under the Freedom of Information Act, 5 U.S.C. 552; therefore, unless NIH/ORDA determines that there are exceptional circumstances, all information submitted in accordance with Appendix M-VII-C will be considered public.

"Reports of serious adverse events may be submitted by e-mail to: ci4e@nih.gov, fax to: 301-496-9839, or by mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010.

Appendix M-VII-C-2, Serious Adverse Event Reporting: Content and Format

"Reports of serious adverse events must follow the format provided in the Adverse Event Reporting Form available on NIH/ORDA's web site at: <http://www.nih.gov/od/orda/>. The serious adverse event report must include, but need not be limited to: (1) The date of the event; (2) a complete description of the event; (3) relevant clinical observations; (4) relevant clinical history; (5) relevant tests that were or are planned to be conducted; (6) the suspected cause of the event; (7) gene delivery method; (8) vector type, e.g., adenovirus; (9) vector subtype, e.g., type 5, relevant deletions; (10) dosing schedule; (11) route of administration; (12) clinical site; (13) principal investigator(s); (14) NIH Protocol number; and (15) Investigational New Drug (IND) number.

"Serious adverse event reports should be stripped of individually-identifiable patient information. Examples of such information include, but are not limited to, the patient's name, address, contact information, social security number, date of birth.

"Appendix M-VII-C-3, Time-Frames for Serious Adverse Event Reporting: Initial and Follow-Up Reports

"Immediate reporting of serious adverse events is essential for the early identification of acute events related to a gene transfer procedure, as well as the identification of patterns that may signal potential safety concerns. For the purposes of the NIH Guidelines, 'immediate' written reporting of

all serious adverse events is to occur as soon as possible but no later than 15 calendar days after such an event has occurred. This applies to all serious adverse events, related or unrelated to gene transfer, which occur during the course of the clinical trial.

"Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. The Principal Investigator(s) must provide any relevant follow-up information to a serious adverse event report within 15 calendar days of receipt of the relevant information. In addition, if a serious adverse event occurs after the end of a clinical trial, and is determined to be related to gene transfer, that event shall be reported by the Principal Investigator within 15 calendar days of the determination."

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which recombinant DNA techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: November 16, 1999.

Lana Skirboll,

*Associate Director for Science Policy,
National Institutes of Health.*

[FR Doc. 99-30342 Filed 11-19-99; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[CA-066-99-1990-00; CACA-20139 and CACA-22901]

Notice of Availability of Supplemental Environmental Impact Statement and Preferred Action for the Proposed Sand and Gravel Mining Operation, Los Angeles County, CA

AGENCY: Bureau of Land Management, Department of the Interior, Palm Springs-South Coast Field Office, Desert District, California.

ACTION: Notice of availability of supplemental environmental impact statement and identification of preferred action.

SUMMARY: In compliance with the National Environmental Policy Act (NEPA) of 1969 and 40 CFR 1503.1(a), notice is hereby given that the Bureau of Land Management (BLM) has prepared a supplement to the Draft Environmental Impact Statement (EIS). This supplement to the Draft EIS addresses a new proposal by Transit Mixed Concrete Company to transport mine material by a conveyor belt system rather than open trucks as proposed in the original draft EIS. The supplement will provide; further analysis of the potential air quality impacts. In addition the supplement identifies the BLM's preferred action. Interested citizens are invited to review the Supplement and submit comments. Copies of the Supplement may be obtained by telephoning or writing to the contact person listed below. Public reading copies of the Supplement are available at the following County of Los Angeles public libraries: Canyon County Library, 18536 Soledad Canyon Road, Santa Clarita, CA 91351; Newhall Library, 22704 W. Ninth Street, Santa Clarita, CA 91321; Valencia Library, 23743 W. Valencia Boulevard, Santa Clarita, CA 91355.

DATES: Comments must be received in writing to the BLM no later than January 10, 2000.

ADDRESSES: Written comments shall be mailed to the following address: Mr. James G. Kenna, Field Manager, Bureau of Land Management, Palm Springs-South Coast Field Office, 690 W. Garnet Avenue, PO Box 1260, North Palm Springs, California, 92258. Comments may also be submitted by electronic mail (E-mail) to the following address: emisquez@ca.blm.gov. The response to comments will be provided in the Final EIS.

FOR FURTHER INFORMATION CONTACT: Ms. Elena Misquez, BLM, Palm Springs-South Coast Field Office, PO Box 1260, North Palm Springs, CA 92258, telephone 760-251-4804.

Dated: November 12, 1999.

Carole Levitzky,

Assistant District Manager, External Affairs.

[FR Doc. 99-30094 Filed 11-19-99; 8:45 am]

BILLING CODE 4310-40-M

DRAFT

PROCLAMATION TO ENSURE THAT
DISCOVERIES FROM THE HUMAN GENOME
ARE USED TO ADVANCE HUMAN HEALTH

In the last decade of the twentieth century, scientists from around the world initiated one of the most significant scientific projects of all time: to determine the DNA sequence of the entire human genome, the human genetic blueprint. Progressing ahead of schedule, human genome research is rapidly advancing our understanding of the causes of human disease and will serve as the foundation for development of a new generation of effective treatments, preventions, and cures. To realize this promise, fundamental data on the human genome, including the human DNA sequence and its variations, must be made freely and broadly accessible to scientists everywhere. The human genome is the fundamental shared heritage of all humankind. Unencumbered access to this information is essential to enable discoveries that will reduce the burden of disease and promote health around the world. We applaud the decision by scientists working on the Human Genome Project to release information about the human DNA sequence and its variants rapidly into the public domain, and we call on all scientists worldwide to adopt this policy.

Discoveries
related
to
genome

stance on
intellectual patent
protection

NAPAS

National Association of Protection & Advocacy Systems

FACSIMILE TRANSMISSION SHEET

Date:

12/2/99

To:

Chris Jennings.

Firm:

White House - Domestic Policy Council

Fax #:

202/456-5557

From:

Shelley Mc Lane

Number of Pages to follow:

2

If you didn't receive the complete number of pages
please call 202-408-9514



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Notes:

Medicare + Genetic Therapy

900 Second Street, NE, Suite 211 Washington, DC 20002 (202) 408-9514

FAX: (202) 408-9520 TTY: (202) 408-9521

Website: <http://www.protectionandadvocacy.com>E-Mail: napas@vipmail.rthlink.net



CONSORTIUM
for
CITIZENS
with
DISABILITIES

December 2, 1999

The White House
Chris Jennings
Deputy Assistant to the President
216 Eisenhower Office Building
1700 Pennsylvania Ave.
Washington, PA 20502

Re: Medicare and Genetic (Biomedical) Technology

Dear Chris,

As I continue to guide the disability community through Medicare reform, I felt it appropriate to provide you with a rationale for integrating genetic technology (and other biomedical advances) into the disability community's position on Medicare.

Genetic therapy has great promise for eliminating chronic disease and decreasing the incidence of disability. As you know, it is still a very high risk clinical trial from recent *Washington Post* reports concerning the September 17th death of Jesse Gelsinger and other issues involved in genetic therapy. Although genetic therapy is still in its infancy, it is important to attempt to extrapolate its potential impact for the Medicare beneficiary population as well as for the broader population.

In the short term with the first generation of gene therapy prescription drugs anticipated to enter the market 2005, it will be important to protect access to these high cost drugs and other gene therapy procedures for Medicare beneficiaries with disabilities. I have read where the commercial market will be creating a third formulary tier in anticipation of high priced, gene therapy prescription drugs. I am requesting that you incorporate these newest business developments into your thinking and planning processes as the Medicare debate continues.

Within the next two decades, I am of the opinion that it will become possible for the medical profession to accurately apply gene therapies to unborn and newborn children in order to diminish the incidence of chronic illness and disability. This will be a wonderful outcome for humanity. The United States will be in a position of having approximately one-third of its population enrolled in the Medicare Program and approximately two-thirds of its population with an extremely low incidence of chronic illness and disability.

However, we have a health care delivery system that survives by segregating the population according to health status, and political currents that wish to apply these principles to the existing Medicare beneficiary population. Segregation of the beneficiary population within the Medicare program is currently underway, but it is absolutely essential to maintain the integrity of the Medicare beneficiary population under one program. If beneficiaries with disabilities are isolated from the rest of the Medicare beneficiary population, there is a danger that they could be further devalued by society as the gene therapy and genetic engineering processes progress. It is for this reason that I am approaching the topic now. **The President's approach of maintaining the Medicare Program as a social insurance program must prevail!** I fear there will be dire consequences in the future for people with disabilities if isolation of the population is allowed to occur in the Medicare program.

Due to the convergence of medical technology, biotechnology, and information technology advances and the exponential growth of global commerce, I am increasingly convinced that we are entering the initial stage of the next phase of evolution of our species (no religious or bioethical connotations intended). It is important that, if you concur, the process is well managed at its initial stage. It would be a legacy that is well remembered for many generations.

Sincerely,



Shelley McLane
Co-Chair Health Task Force

Senior Public Policy Analyst
NAPAS

of Jesse Gelsinger

Ever since it became a reality nine years ago,

gene therapy has been
the bright promise of medicine.

Then an experiment went very wrong.

By Sheryl Gay Stolberg



THE JAGGED PEAK of Mount Wrightson towers 9,450 feet above Tucson, overlooking a deep gorge where the prickly pear cactus that dots the desert floor gives way to a lush forest of ponderosa pine. It is said that this is as close to heaven as you can get in southern Arizona. Jesse Gelsinger loved this place. So it was here, on a clear Sunday afternoon in early November, that Paul Gelsinger laid his 18-year-old son to rest, seven weeks after a gene-therapy experiment cost him his life.

The ceremony was simple and impromptu. Two dozen mourners — Jesse's father; his mother, Pattie; his stepmother, Mickie; and two sisters, a brother, three doctors and a smattering of friends — trudged five miles along a steep trail to reach the rocky outcropping at the top. There, Paul Gelsinger shared stories of his son, who loved motorcycles and professional wrestling and was, to his father's irritation, distinctly lacking in ambition. Jesse was the kind of kid who kept \$10.10 in his bank account — "You need \$10 to keep it open," Gelsinger explained — but those assembled on the mountaintop agreed that he had a sharp wit and a sensitive heart.

At Gelsinger's request, the hikers had carried Jesse's medicine bottles filled with his ashes, and now they were gathered at the edge of the peak. Steve Raper, the surgeon who gave Jesse what turned out to be a lethal injection of new genes, pulled a small blue book of poetry from his pocket. "Here rests his head upon the lap of Earth," Raper read, reciting a passage from an elegy by Thomas Gray, "a youth to Fortune and Fame unknown./Fair Science frowned not on his humble birth." Then the surgeon, the grieving father and the rest scattered Jesse's ashes into the canyon, where they rose on a gust of wind and fell again in a powerful cloud of fine gray dust. "I will look to you here often, Jess," Paul Gelsinger said sadly.

Jesse Gelsinger was not sick before he died. He suffered from ornithine transcarbamylase (OTC) deficiency, a rare metabolic disorder, but it was controlled with a low-

protein diet and drugs, 32 pills a day. He knew when he signed up for the experiment at the University of Pennsylvania that he would not benefit; the study was to test the safety of a treatment for babies with a fatal form of his disorder. Still, it offered hope, the promise that someday Jesse might be rid of the cumbersome medications and diet so restrictive that half a hot dog was a treat. "What's the worst that can happen to me?" he told a friend shortly before he left for the Penn hospital, in Philadelphia. "I die, and it's for the babies."

As far as government officials know, Jesse's death on Sept. 17 was the first directly related to gene therapy. The official cause, as listed on the death certificate filed by Raper, was adult respiratory distress syndrome: his lungs shut down. The truth is more complicated. Jesse's therapy consisted of an infusion of corrective genes, encased in a dose of weakened cold virus, adenovirus, which functioned as what scientists call a vector. Vectors are like taxicabs that drive healthy DNA into cells; viruses, whose sole purpose is to get inside cells and infect them, make useful vectors. The Penn researchers had tested their vector, at the same dose Jesse got, in mice, monkeys, baboons and one human patient, and had seen expected, flulike side effects, along with some mild liver inflammation, which disappeared on its own. When Jesse got the vector, he suffered a chain reaction that the testing had not predicted — jaundice, a blood-clotting disorder, kidney failure, lung failure and brain death: in Raper's words, "multiple-organ-system failure." The doctors are still investigating; their current hypothesis is that the adenovirus triggered an overwhelming inflammatory reaction — in essence, an immune-system revolt. What they do not understand yet is why.

Every realm of medicine has its defining moment, often with a human face attached. Polio had Jonas Salk. In vitro fertilization had Louise Brown, the world's first test-tube baby. Transplant surgery had Barney Clark, the Seattle



Jesse, feeling victorious, the day after he underwent testing and found out he would be eligible for the gene-therapy experiment.

dentist with the artificial heart. AIDS had Magic Johnson. Now gene therapy has Jesse Gelsinger.

Until Jesse died, gene therapy was a promising idea that had so far failed to deliver. As scientists map the human genome, they are literally tripping over mutations that cause rare genetic disorders, including OTC deficiency, Jesse's disease. The initial goal was simple: to cure, or prevent, these illnesses by replacing defective genes with healthy ones. Biotech companies have poured millions into research — not for rare hereditary disorders but for big-profit illnesses like cancer, heart disease and AIDS. As of August, the government had reviewed 331 gene-therapy protocols involving more than 4,000 patients. Just 41 were for the "monogeneic," or single-gene, defect diseases whose patients so desperately hoped gene therapy would be their salvation.

At the same time, the science has progressed slowly; researchers have had trouble devising vectors that can carry genes to the right cells and get them to work once they are there. Four years ago, Dr. Harold Varmus, the director of the National Institutes of Health, commissioned a highly critical report about gene therapy, chiding investigators for creating "the mistaken and widespread perception of success." Since then, there have been some accomplishments: a team at Tufts University has used gene therapy to grow new blood vessels for heart disease patients, for instance. But so far, gene therapy has not cured anyone. As Ruth Macklin, a bioethicist and member of the Recombinant DNA Advisory Committee, the National Institutes of Health panel that oversees gene-therapy research, says, bluntly, "Gene therapy is not yet therapy."

On Dec. 8, the "RAC," as the committee is called, will begin a public inquiry into Jesse's death, as well as the safety of adenovirus, which has been used in roughly one-quarter of all gene-therapy clinical trials. The Penn scientists will report on their preliminary results, and investigators, who at the RAC's request have submitted thousands of pages of patient safety data to the

committee, will discuss the side effects of adenovirus. Among them will be researchers from the Schering-Plough Corporation, which was running two experiments in advanced liver cancer patients that used methods similar to Penn's. Enrollment in those trials was suspended by the Food and Drug Administration after Jesse's death. The company, under pressure from the RAC, has since released information showing that some patients experienced serious side effects, including changes in liver function and blood-cell counts, mental confusion and nausea; two experienced minor strokes, although one had a history of them. Once all the

data on adenovirus are analyzed at the Dec. 8 meeting, the RAC may recommend restrictions on its use, which will almost certainly slow down some aspects of gene-therapy research.

The meeting will be important for another reason: it will mark an unprecedented public airing of information about the safety of gene therapy — precisely the kind of sharing the RAC has unsuccessfully sought in the past. Officials say gene therapy has claimed no lives besides Jesse's. But since his death, there have been news reports that other patients died during the course of experiments — from their diseases, as opposed to the therapy — and that the scientists involved did not report those deaths to the RAC, as is required. This has created a growing cloud of suspicion over gene therapy, raising questions about whether other scientists may have withheld information that could have prevented Jesse's death. That question cannot be answered until all the data are analyzed. But one thing is certain: four years after the field was rocked by Varmus's highly critical evaluation, it is now being rocked again, this time over an issue more fundamental than efficacy — safety.

"I think it's a perilous time for gene therapy," says LeRoy Walters, a bioethicist at Georgetown University and former chairman of the RAC. "Until now, we have been able to say, 'Well, it hasn't helped many people, but at least it hasn't hurt people.' That has changed."

NO ONE, PERHAPS, is more acutely aware of gene therapy's broken promise than Mark Batshaw, the pediatrician who proposed the experiment that cost Jesse Gelsinger his life.

At 54, Batshaw, who left the University of Pennsylvania last year for Children's National Medical Center, in Washington, is tall and gangly with slightly stooped shoulders and a shy smile that gives him the air of an awkward schoolboy, which he once was. As a child, Batshaw struggled with hyperactivity: he didn't read until the third grade; in the fourth, his teacher grew so irritated at his constant chatter that she stuck his chair out in the hall. The experience has left him with a soft spot for developmentally disabled

children, which is how he has become one of the world's foremost experts in urea-cycle disorders, among them OTC deficiency.

The urea cycle is a series of five liver enzymes that help rid the body of ammonia, a toxic breakdown product of protein. When these enzymes are missing or deficient, ammonia — "the same ammonia that you scrub your floors with," Batshaw explains — accumulates in the blood and travels to the brain, causing coma, brain damage and death. OTC deficiency is the most common urea-cycle disorder, occurring in one out of every 40,000 births. Its genetic mutation occurs on the X chromosome, so women are typically carriers, while their sons suffer the disease.

Severe OTC deficiency is, Batshaw says, "a devastating disease." Typically, newborns slip into a coma within 72 hours of birth. Most suffer severe brain damage. Half die in the first month, and half of the survivors die by age 5. Batshaw was a young postdoctoral fellow when he met his first urea-cycle-disorder patient in 1973, correctly diagnosing the disease at a time when most other doctors had never heard of it. Within two years, he and his colleagues had devised the first treatment, a low-protein formula called keto-acid. Later, they came up with what remains standard therapy to this day: sodium benzoate, a preservative, and another type of sodium, which bind to ammonia and help eliminate it from the body.

But the therapy cannot prevent the coma that is often the first sign of OTC and ravages the affected infant. By the time Batshaw joined the faculty at Penn in 1988, he was dreaming of a cure — gene therapy. Patients were dreaming, too, says Tish Simon, former co-president of the National Urea Cycle Disorders Foundation, whose son died of OTC deficiency three years ago. "All of us saw gene therapy as the hope for the future," Simon says. "And certainly, if anybody was going to do it, it had to be Mark Batshaw."

GENE THERAPY BECAME A REALITY ON SEPT. 14, 1990, in a hospital room at the National Institutes of Health, in Bethesda, Md., when a 4-year-old girl with a severe immune-system deficiency received a 30-minute infusion of white blood cells that had been engineered to contain copies of the gene she lacked. Rarely in modern medicine has an experiment been filled with so much hope; news of the treatment ricocheted off front pages around the world. The scientist who conducted it, Dr. W. French Anderson, quickly became known as the father of gene therapy. "We had got ourselves all hyped up," Anderson now admits, "thinking there would be rapid, quick, easy, early cures."

Among those keeping a close eye on Anderson's debut was Jim Wilson, a square-jawed, sandy-haired Midwesterner who decided to follow his father's footsteps in medicine when he realized he wasn't going to make it in football. As a graduate student in biological chemistry,

Sheryl Gay Stolberg, who reports on medicine and health policy for The Times, wrote about pig-to-human organ transplants in October.

Wilson had taken a keen interest in rare genetic diseases. "All I did," he says, "was dream about gene therapy."

Today, as director of the Institute for Human Gene Therapy at the University of Pennsylvania, Wilson is in an excellent position to make that dream a reality. Headquartered in a century-old building amid the leafy maple trees and brick sidewalks of the picturesque Penn campus, the six-year-old institute, with 250 employees, state-of-the-art laboratories and a \$25 million annual budget, is the largest academic gene-therapy program in the nation. In a field rife with big egos, Wilson is regarded as first-rate. "Present company excluded," Anderson says, "he's the best person in the field."

Batshaw was banging on Wilson's door even before Wilson arrived at Penn in March 1993, and within a month they were collaborating on studies of OTC-deficient mice. Their first task was to develop a vector. Adenovirus seemed a logical choice.

There had been some early problems with safety — a 1993 cystic fibrosis experiment was shut down when a patient was hospitalized with inflamed lungs — but Wilson and Batshaw say they figured out how to make a safer vector by deleting extra viral genes. Adenovirus was the right size: when its viral genes were excised, the OTC gene fit right in. It had a "ZIP code," on it, Batshaw says, that would carry it straight to the liver. And while its effects did not last, it worked quickly, which meant that it might be able to reverse a coma, sparing babies from brain damage. "It wasn't going to be a cure soon," Batshaw says, "but it might be a treatment soon."

The mouse experiments were encouraging. Mice that had the therapy survived for two to three months even while fed a high-protein diet. Those that lacked the treatment died. "It wasn't subtle," Wilson says. "We felt pretty compelled by that." But when the team contemplated testing in people, they ran smack into an ethical quandary: who should be their subjects?

To Wilson, the answer seemed obvious: sick babies. Arthur Caplan, the university's resident bioethics expert, thought otherwise. Caplan says parents of dying infants are incapable of giving informed consent: "They are coerced by the disease of their child." He advised Wilson to test only stable adults, either female carriers or men like Jesse, with partial enzyme deficiencies. The National Urea Cycle Disorders Foundation agreed. When Batshaw turned up at their 1994 annual meeting asking for volunteers, so many mothers offered to be screened for the OTC gene that it took him four hours to draw all the blood.

BY THE TIME MARK Batshaw and Jim Wilson submitted their experiment to the Recombinant DNA Advisory Committee for approval, the panel was in danger of being disbanded. Varmus, the N.I.H. director, who won the Nobel Prize for his discovery of a family of

cancer-causing genes, had made no secret of his distaste for the conduct of gene-therapy researchers. He thought the science was too shoddy to push forward with human testing, and it bothered him that so few experiments were focusing on genetic diseases. It irked him to have to sign off on protocols the RAC approved, and it irked him even more to see biotech companies touting those approvals, like some kind of N.I.H. imprimatur, in the business pages of the papers. "Some days," says Dr. Nelson Wivel, the committee's former executive director, who now works for Wilson at Penn, "it felt as though the RAC was helping the biotech industry raise money. Dr. Varmus hated that."

At the same time, the pharmaceutical industry and AIDS activists were complaining that the RAC was redundant: the F.D.A. already reviewed gene-therapy proposals. So in mid-1995, after seeking the advice of an expert panel, Varmus reorganized the RAC, slashing its membership

"What's the worst that can happen to me?"
Jesse told a friend, shortly before he left for the hospital in
Philadelphia. "I die, and it's for the babies."

from 25 to 15 and stripping it of its approval authority — a decision that, some say, has enabled gene-therapy researchers to ignore the panel and keep information about safety to themselves. "The RAC," complains Dr. Robert Erickson, a University of Arizona medical geneticist who served on the panel, "became a debating society."

The Batshaw-Wilson protocol was among the last the committee would ever approve. The plan was for 18 adults (19 eventually signed up, including Tish Simon, but the last patient was never treated, because of Jesse's death) to receive an infusion of the OTC gene, tucked inside an adenovirus vector, through a catheter in the hepatic artery, which leads to the liver. The goal was to find what Wilson calls "the maximum tolerated dose," one high enough to get the gene to work, but low enough to spare patients serious side effects. Subjects would be split into six groups of three, with each group receiving a slightly higher dose than the last. This is standard fare in safety testing. "You go up in small-enough increments," Wilson explains, "that you can pull the plug on the thing before people get hurt."

The experiment stood in stark contrast to others that had earned Varmus's scorn. It was paid for by N.I.H., which meant it had withstood the rigors of scientific peer review. It was aimed at a rare genetic disease, not cancer or AIDS. It was supported by plenty of animal research: Wilson and his team had performed more than 20 mouse experiments to test efficacy and a dozen safety studies on mice, rhesus monkeys and baboons. Still, it made Erickson, one of two scientists assigned by the RAC to review the experiment, uneasy.

He was troubled by data showing that three monkeys had died of a blood-clotting disorder

and severe liver inflammation when they received an earlier, stronger version of the adenovirus vector at a dose 20 times the highest dose planned for the study. No one had injected adenovirus directly into the bloodstream before, either via the liver or otherwise, and the scientists admitted that it was difficult to tell precisely how people would respond. They planned to confine the infusion to the right lobe of the liver, so that if damage occurred it would be contained there, sparing the left lobe. And they outlined the major risks: bleeding, from either the gene-therapy site or a subsequent liver biopsy, which would require surgery; or serious liver inflammation, which could require an organ transplant and might lead to death.

Both Erickson and the other scientific reviewer thought the experiment was too risky to test on asymptomatic volunteers and recommended rejection. But in the end, Batshaw and Wilson prevailed. They offered up Caplan's argument that

testing on babies was inappropriate. And they agreed to inject the vector into the bloodstream, as opposed to putting it directly into the liver. That decision, however, was later reversed by the F.D.A., which insisted that because the adenovirus would travel through the blood and wind up in the liver anyway, the original plan was safer.

The RAC, in such disarray from Varmus's reorganization that it did not meet again for another year, was never informed of the change.

JESSE GELSINGER WAS 17 WHEN HIS PEDIATRIC geneticist, Dr. Randy Heidenreich, first told him about the Penn proposal. He wanted to sign up right away. But he had to wait until he was 18.

Paul Gelsinger was also enthusiastic. A trim 47-year-old with intense blue eyes, Gelsinger, who makes his living as a handyman, gained custody of his four children nine years ago, when he divorced their mother, who suffers from manic depression. He had been having some difficulty with Jesse then; the boy was in the midst of an adolescent rebellion and was refusing to take his medicine. "I said: 'Wow, Jess, they're working on your disorder. Maybe they'll come up with a cure.'"

Jesse's was not a typical case of OTC deficiency: his mutation appears to have occurred spontaneously in the womb. His disease having been diagnosed when he was 2, Jesse was what scientists call a mosaic — a small portion of his cells produced the missing enzyme. When he watched what he ate and took his medicine, he was fine. But one day last December, Paul Gelsinger arrived home to find his son curled up on the couch. He had been vomiting uncontrollably, a sign, Paul knew, that Jesse's ammonia was rising. Jesse landed in the hospital, comatose and on life

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support. When he recovered, he never missed another pill.

On June 18, the day Jesse turned 18, the Gelsingers — Paul, Mickie and the children — flew to Philadelphia to see Paul's family. They played tourists, visiting the Liberty Bell and the Rocky statue, where Jesse was photographed, fists raised, a picture that would circulate in the newspapers after his death. On the 22nd, they went to the University of Pennsylvania, where they met Raper, the surgeon, who explained the experiment and did blood and liver-function tests to see if Jesse was eligible. He was, and his treatment was scheduled for the fall. Jesse would be the youngest patient enrolled.

On Sept. 9, Jesse returned to Philadelphia, this time alone. He took one duffel bag full of clothes and another full of wrestling videos. Paul Gelsinger planned to fly in a week later for the liver biopsy, which he considered the trial's most serious risk.

The treatment began on Monday, Sept. 13. Jesse would receive the highest dose. Seventeen patients had already been treated, including one woman who had been given the same dose that Jesse would get, albeit from a different lot, and had done "quite well," Raper says. That morning, Jesse was taken to the interventional-radiology suite, where he was sedated and strapped to a table while a team of radiologists threaded two catheters into his groin. At 10:30 a.m., Raper drew 30 milliliters of the vector and injected it slowly. At half past noon, he was done.

That night, Jesse was sick to his stomach and spiked a fever, 104.5 degrees. Raper was not particularly surprised: other patients had experienced the same reaction. Paul Gelsinger called; he and Jesse talked briefly, exchanging I love yous. Those were the last words they ever spoke.

Early Tuesday morning a

nurse called Raper at home; Jesse seemed disoriented. When Raper got to the hospital, about 6:15 a.m., he noticed that the whites of Jesse's eyes were yellow. That meant jaundice, not a good sign. "It was not something we had seen before," Raper says. A test confirmed that Jesse's bilirubin, a breakdown product of red blood cells, was four times the normal level. Raper called Gelsinger, and Batshaw in Washington, who said he would get on a train and be there in two hours.

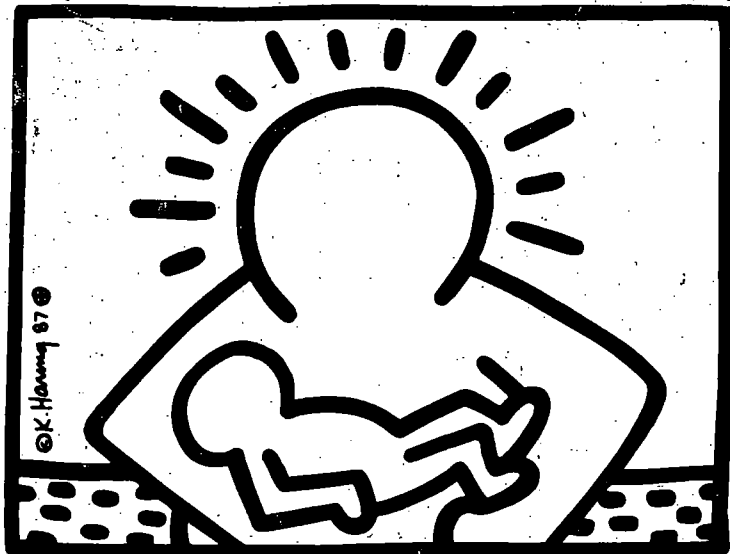
Both doctors knew that the high bilirubin meant one of two things: either Jesse's liver was failing or he was suffering a clotting disorder in which his red blood cells were breaking down faster than the liver could metabolize them. This was the same disorder the scientists had seen in the monkeys that had been given the stronger vector. The condition is life-threatening for anyone, but particularly dangerous for someone with Jesse's disease, because red blood cells liberate protein when they break down.

By midafternoon Tuesday, a little more than 24 hours after the injection, the clotting disorder had pushed Jesse into a coma. By 11:30 p.m., his ammonia level was 393 micromoles per liter of blood. Normal is 35. The doctors began dialysis.

Paul Gelsinger had booked a red-eye flight. When he arrived in the surgical intensive care unit at 8 Wednesday morning, Raper and Batshaw told him that dialysis had brought Jesse's ammonia level down to 72 but that other complications were developing. He was hyperventilating, which would increase the level of ammonia in his brain. They wanted to paralyze his muscles and induce a deeper coma, so that a ventilator could breathe for him. Gelsinger gave consent. Then he put on scrubs, gloves and a mask and went in to see his son.

By Wednesday afternoon,
Continued on Page 149

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GENE THERAPY

Continued from Page 140

Jesse seemed to be stabilizing. Batshaw went back to Washington. Paul felt comfortable enough to meet his brother for dinner. But later that night Jesse worsened again. His lungs grew stiff; the doctors were giving him 100 percent oxygen, but not enough of it was getting to his bloodstream. They consulted a liver-transplant team and learned that Jesse was not a good candidate. Raper was beside himself. He consulted with Batshaw and Wilson, and they decided to take an extraordinary step, a procedure known as ECMO, for extracorporeal membrane oxygenation, essentially an external lung that filters the blood, removing carbon dioxide and adding oxygen. It had been tried on only 1,000 people before, Raper says. Only half had survived.

"If we could just buy his

lungs a day or two," Raper said later, they thought "maybe he would go ahead and heal up."

The next day, Thursday, Sept. 16, Hurricane Floyd slammed into the East Coast. Mickie Gelsinger flew in from Tucson just before the airport closed. (Pattie Gelsinger, Jesse's mother, was being treated in a psychiatric facility and was unable to leave.) Batshaw spent the day trapped outside Baltimore on an Amtrak train. He ran down his cell phone calling Raper; when it went dead, he persuaded another passenger to lend him his. The ECMO, Raper reported, appeared to be working. But then another problem cropped up: Jesse's kidneys stopped making urine. "He was sliding into multiple-organ-system failure," Raper says.

That night, at his hotel, Paul Gelsinger couldn't sleep. He left his wife a note

and walked the half mile to the Penn medical center to see Jesse. The boy was bloated beyond recognition; even his ears were swollen shut. Gelsinger noticed blood in Jesse's urine, an indication, he knew, that the kidneys were shutting down. How can anybody, he thought, survive this?

On the morning of Friday the 17th, a test showed that Jesse was brain dead. Paul Gelsinger didn't need to be told: "I knew it already." He called for a chaplain to hold a bedside service, with prayers for the removal of life support.

The room was crowded with equipment and people: 7 of Paul's 15 siblings came in, plus an array of doctors and nurses. Raper and Batshaw, shellshocked and exhausted, stood in the back. The chaplain anointed Jesse's forehead with oil, then read the Lord's Prayer. The doctors fought back tears.

When the intensive-care specialist flipped two toggle switches, one to turn off the ventilator and the other to turn off the ECMO machine, Raper stepped forward. He checked the heart-rate monitor, watched the line go flat and noted the time: 2:30 p.m. He put his stethoscope to Jesse's chest, more out of habit than necessity, and pronounced the death official. "Goodbye, Jesse," he said. "We'll figure this out."

WILSON REPORTED THE death immediately, drawing praise from government officials but criticism from Arthur Caplan, who says they should have made the news public, in a news conference. In the weeks since, the Penn team has put every detail of Jesse's treatment under a microscope. It has rechecked the vector to make certain it was not tainted, tested the same lot on monkeys, re-

examined lab and autopsy findings. Wilson's biggest fear was that Jesse died as a result of human error, but so far there has been no evidence of that. "That's what's so frightening," French Anderson says. "If they made a mistake, you would feel a little safer."

The death has rattled the three doctors in various ways. Wilson has asked himself over and over again whether he should have done anything differently. "At this point, I say no, but I'm continuing to re-evaluate constantly." He has been besieged by worry, about the morale of his staff, about whether his institute's financial sponsors would pull out, about whether patients would continue to volunteer, about whether he would lose his bravado — the death knell for a scientist on the cutting edge. "My concern," he confessed, over dinner one

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night in Philadelphia, "is, I'm going to get timid, that I'll get risk averse."

Raper has thrown himself into his work, trying to live up to his promise to "figure this out." There are a number of possible explanations, he says: the vector may have reacted badly with Jesse's medication; Jesse's status as a mosaic may have played a role; or perhaps the early testing in monkeys, which showed that the stronger vector had deleterious side effects, was more of a harbinger of danger than the doctors realized. An answer may take months, but he is determined to find one; only by understanding what happened to Jesse, and how to prevent it in others, can the research continue. "That," Raper says, "would be the best tribute to Jesse."

Of the three, Batshaw seems to have taken it the hardest. He is not a particularly religious man, but a few days after Jesse died he went to synagogue to say Kaddish, the Jewish mourner's prayer. He struggles with the idea of personal responsibility. He has cradled many a dying child in his career, but never before, he says, has a patient been made worse by his care. "What is the Hippocratic oath?" Batshaw asks rhetorically, looking into the distance as his fingers drum the tabletop. He pauses, as if to steel himself, and says, "I did harm."

Paul Gelsinger does not hold the doctors responsible, although he is acutely interested in knowing what other scientists knew about adenovirus before Jesse died. He has experienced a deep spiritual awakening since losing his son; in dying, he says, Jesse taught him how to live. He speaks frequently of God, and of "purity of intent," which is his way of saying that Jesse demonstrated an altruism the rest of us might do well to emulate. "I hope," he said on the mountaintop that Sunday afternoon, "that I can die as well as my son has died." ■



DEPARTMENT OF HEALTH & HUMAN SERVICES

Chief of Staff

Washington, D.C. 20201

FACSIMILE

DATE: 2-24

TO: Deborah Adler

FAX#: 456-5557

FROM: Mary Beth Donahue
Chief of Staff

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

COMMENTS:

Deborah - final as promised.
Eileen

2 Pages [including this cover]

The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) are committed to working together to minimize the risks of gene transfer trials and ensure that patients are fully informed of such risks. We are collaborating on the following new initiatives to ensure that gene transfer clinical trials are safe and in compliance with Federal guidelines and regulations.

Sharing of Adverse Event Reports to Ensure Investigator Compliance

- NIH and FDA implemented two new Standard Operating Procedures and Policies (SOPP), to ensure that adverse event reports are shared between the agencies.

NIH Site Visits to Enhance Investigator Compliance

- NIH will make a series of site visits to institutions to monitor compliance with a range of NIH rules, regulations, and guidelines, including the NIH Guidelines and policies relevant to gene transfer research.

Additional FDA Inspections.

- The FDA will conduct more inspections to increase oversight of gene therapy Investigational New Drug applications (INDs).

Comprehensive Review of NIH's Role in Gene Therapy Oversight.

- A working group of the Advisory Committee to the Director, NIH (ACD), composed of individuals from outside the Federal government, has been established to conduct a review of NIH's role in the oversight of clinical gene transfer.

Enhancing Public Access to Information about Gene Transfer Research.

- By the end of the year 2000, NIH will complete an interactive Web-based database of gene transfer protocols and adverse event reports.
- The FDA will issue a proposed rule on the public disclosure of information regarding gene transfer clinical trials that would provide more information on these trials to the general public.

Educational Outreach Programs.

- The NIH and the FDA are sponsoring additional educational outreach programs to ensure that all investigators, sponsors, and institutions involved in gene transfer research understand the guidelines and regulations concerning gene transfer clinical trials.



F A C S I M I L E

DATE: 2/23/00

TO: Chris Jennings

FAX#: 456-5557

FROM: Mary Beth Donahue
Chief of Staff

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

COMMENTS:

*Kirschstein's Letter
to Waxman*

2 Pages [including this cover]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

February 23, 2000

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

Dear Mr. Waxman:

This letter is a preliminary response to the letter I received from you this afternoon in regard to gene therapy trials. At the outset, let me state that the National Institutes of Health (NIH) staff made extraordinary efforts to respond to your questions and requests for information. This was a difficult task, given that NIH staff were also working collaboratively with our colleagues at the Food and Drug Administration (FDA) to enact important reforms in the oversight process. It is my understanding that your office received everything you requested, and in a timely manner. I also understand that you were provided with all the adverse event reports submitted since the inception of gene transfer research more than a decade ago.

Among the cases cited in your letter are events involving gene transfer trials using adenoviral vectors. These cases were reviewed and appropriately addressed by the NIH. In this regard, in December 1999, in response to the death of a participant in a gene transfer trial at the University of Pennsylvania, the NIH convened a special working group of the Recombinant DNA Advisory Committee (RAC) to review all adverse events pertaining to gene therapy trials using adenoviral vectors that had been reported to NIH. The working group, comprised of some of the most eminent scientists in the world, comprehensively reviewed the data. They concluded that there were no significant and unanticipated risks, in these trials or in any others, that would preclude the cautious continuation of this important line of clinical research.

Non-compliance by investigators with the *NIH Guidelines* requirement for reporting adverse events is unacceptable. We have instituted aggressive oversight procedures, and are taking all necessary measures to ensure compliance with our *Guidelines*. Several of the remedies already in place are enclosed. Also, pursuant to a request from the President, NIH is working with FDA to accelerate our review of federal oversight of this class of research.

We are working on a more detailed response to your letter. Please contact me if you have any additional questions.

Sincerely,

Ruth L. Kirschstein, M.D.
Acting Director

Enclosure

Congress of the United States House of Representatives

Washington, DC 20515-0529

HENRY A. WAXMAN

29TH DISTRICT, CALIFORNIA February

23, 2000

Dr. Ruth Kirschstein Acting
Director

National Institutes of Health

Bethesda, Maryland 20892

Dear Dr. Kirschstein

I am writing to let you know of my deep concern about the adverse event data from gene therapy trials overseen by the National Institutes of Health (NIH). This new information shows an compliance with NIH gene therapy guidelines and suggests that NIH's oversight has inexplicable none been inadequate.

As you know, I first wrote requesting information about adverse event reports in November 1999. Since then, I have been surprised and disappointed by the NIH's lack of cooperation in sharing information and supplying constructive analysis. In fact, it has been extraordinarily difficult and time-consuming simply to receive a complete accounting of both the adenoviral and non-adenoviral gene therapy trial protocols.

Despite these obstacles, my staff—with the assistance of the minority staff of the House Commerce Committee—have conducted a preliminary review of the NIH's gene therapy adverse event reports and have identified that many of the adverse event reports are not being reported to the NIH concerning the deaths, life-threatening events, and injuries taking place in their research. Moreover, the reports received by the NIH in response to its October 1 and November 22, 1999, appeals for adverse event data were frequently incomplete or undated.

The most recent reports raise new questions about the conduct of gene therapy trials, the apparent compliance, and the problems of federal oversight. Three trials, in particular, illustrate the

- In one trial, a 1996 patient death was reported and lab tests were promised to assure no causal relation to the gene therapy. But no results were apparently provided by the investigator or sought by the NIH, even after your agency's 1999 appeals for information.
- One trial—of the many that continually provided no reports to the NIH—stands out because 38 of its 48 patients "die[d] between study initiation and completion" and it had "1.112 [adverse] events of which 281 were considered related to treatment."

HHS will respond w/
the letter undraft.
A fuller response
will go by March 1
(per Rich).

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NIH Acting Director Ruth Kirschstein, M.D.

February 23, 2000

Page 2

- In a third trial, an NIH pharmacy shipped the wrong medication, which was actually administered to patients in a gene therapy trial. Yet no information was provided on how the NIH's error was discovered or the agency's plans to prevent such potentially life-threatening failures in the future.

Given my recent experiences with your agency, I am skeptical that additional information can help explain why the NIH didn't adequately investigate the 1996 death of one patient, why it shipped the wrong medication to some patients, or why it didn't take any action in a trial that resulted in the death of three out of every four patients participating in it. Nonetheless, it is important for Congress to try to have as much information as possible, so I would appreciate receiving your response to the following questions and any mitigating facts that you believe may provide a context for these intolerable incidents.

- A. Trial 9212-035 - "Gene Therapy of Cystic Fibrosis Using E1 Deleted Adenovirus: A Phase I Study" - James M. Wilson, University of Pennsylvania Medical Center; Richard H. Simon, University of Michigan Medical Center; Karen McCoy, Ohio State University

On March 11, 1996, University of Pennsylvania researchers wrote a brief three-paragraph letter to NIH Office of Recombinant DNA Activities (ORDA) Director Nelson Wivel "to report the death of one of our patients." The letter states: "Lung tissue has been harvested and the Institute is currently running tests for expression of gene transfer and adenovirus persistence. We will forward these results to you as soon as they are available."¹

One of the NIH's most fundamental responsibilities is to ensure that an experimental treatment doesn't cause the death of patients. I don't see any information in the record, however, that indicates any scrutiny of a possible causal relationship between the trial's treatment and the patient's death. If so, this would be an egregious failure by the NIH.

To help clarify these issues, please respond to the following questions:

- Did the NIH receive the test results in 1996? If not, were they included in the Penn Institute for Human Gene Therapy's October 20, 1999 submission of summary data for all of its gene therapy trials?
- If the test results still have not been submitted by the Penn Institute, do you agree that this represents a glaring oversight in the exercise of the NIH's responsibilities? What steps has the NIH taken to obtain the results? And is the NIH now actively investigating a causal relationship between the gene therapy and the patient's death?
- What impact did the unprecedented hiatus in the Recombinant DNA Advisory Committee's (RAC) oversight following NIH Director Varmus' 1996 decision to abolish it have on the lack of documented follow-up by the NIH in 1996? What impact did the turnover in NIH Office of Recombinant DNA Activities (ORDA) personnel have on NIH follow-up?

¹ Letter from Dr. James M. Wilson and Dr. Cynthia Robinson to Dr. Nelson A. Wivel (March 1996).

NIH Acting Director Ruth Kirschstein, M.D.

February 23, 2000

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B. Trial 9406-079 - "A Tolerance and Efficacy Study of Increasing Doses of Adenoviral Vector Expressing Wildtype p53 Administered with Cisplatin in Patients with Non-Small Cell Lung Cancer" - Jack A. Roth and John Nemunaitis, M.D. Anderson Cancer Center

In its October 22, 1999 summary report to the NIH, Introgen Therapeutics disclosed that, of the total 48 patients in this trial, 38 "died between study initiation and completion," "35 serious adverse events were experienced by 28 patients" and "there were 1112 total [other] events of which 281 were considered related to treatment."²

It would seem obvious that there would be vigorous and immediate oversight of any protocol that results in the deaths of 75% of the participating patients. There is no indication, however, that the NIH has taken any action in this matter. Does the NIH believe that the severity of the disease being investigated explains the trial's high mortality and justifies the apparent lack of follow-up activity by the agency? In addition, please respond to the following:

- When did the NIH first learn of these 38 deaths?
- Did the NIH consider the large number of deaths unusual and of concern? What has the NIH done to investigate this matter?
- The information on the 35 serious adverse events, as well as the patient deaths "possibly related" to the therapy, is brief and provided only in summary form. Does the NIH consider this information adequate to confirm whether the sponsor's judgments regarding causation are accurate?
- The summary of adverse events was apparently provided to the NIH three years after they occurred by the corporate sponsor of this trial. Was there an earlier indication of problems by the investigators of the study? If not, and investigators violated the NIH Guidelines, did the corporate sponsor have a responsibility to inform you in a more timely manner? If you do not view the corporate sponsor as responsible, what steps need to be taken to ensure responsibility in such instances?

C. Trial 9706-193 - "A Phase 1 / 2 Study of Sequential Vaccinations with Vaccinia CEA and ALVAC CEA with the Addition of IL-2 and GM-CSF in Patients with CEA Expressing Tumors" - James L. Marshall, Georgetown University Medical Center

On December 8, 1999, a National Cancer Institute (NCI) pharmacy shipped the wrong medication to Georgetown University Hospital, where it was administered to six patients in a gene therapy trial. On December 27, Dr. James Marshall informed the FDA that "[s]ix patients who were enrolled" in the NIH-sponsored gene therapy trial "were administered ALVAC IL-12 instead of ALVAC CEA."³

² Introgen Therapeutics, *Adenoviral Vector Safety and Toxicity Reporting Form* (October 21, 1999).

³ Letter to FDA CBER Director of Vaccines Research and Review Karen Goldenthal from Dr. John L. Marshall (December 27, 1999).

NIH Acting Director Ruth Kirschstein, M.D.

February 23, 2000

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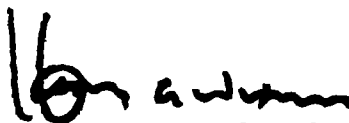
Providing the wrong medication to patients is an act of inexcusable incompetence. The fundamental question is whether this was an isolated instance or whether other similar mistakes are possible. To address this issue, please respond to the following:

- What is your explanation for the mistake made by the NIH? Was there a second mistake by Georgetown University in failing to recognize the problem?
- The NIH data do not disclose how the NCI discovered the error or whether the NCI computer failure resulted in other dispensing and shipping errors for other protocols or patients. Nor does the data include the agency's plans to prevent such potentially life-threatening failures in the future. Please provide this information.
- Georgetown University Hospital convened an internal review committee to implement steps to prevent such medication errors in the future. Dr. Marshall reported, "The findings [of] that committee will be forwarded once the special report has been completed in January 2000." As of February 9, however, your agency had apparently either failed to receive the report or did not make it available. Please explain this and provide a copy of the report.
- Are you aware of other trials that resulted in mistakes in administering medication?

The sheer volume and variety of noncompliance with the NIH Guidelines evident in the gene therapy serious adverse event data is extremely troubling in itself. It also underscores, however, the absolute need not only for federal regulation, but for federal regulation that is competent and comprehensive.

Thank you for your assistance, and please ensure that I receive your response by March 1.

Sincerely,



HENRY A. WAXMAN
Member of Congress

cc: The Honorable Donna Shalala
Secretary of Health and Human Services

TOTAL P.25

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View Related Topics

April 28, 2000, Friday, Late Edition - Final

SECTION: Section A; Page 21; Column 5; National Desk

LENGTH: 645 words

HEADLINE: Death of Infant Is Linked To Hospital Study of a Drug

BYLINE: AP

DATELINE: PITTSBURGH, April 27

BODY:

A hospital study designed to test a heartburn remedy on children was partly to blame for the death of a 9-month-old boy, the Allegheny County coroner has ruled.

When the boy died in November, the coroner, Cyril Wecht, said the cause was sudden infant death syndrome. But on Tuesday, Dr. Wecht amended the death certificate to say that the inclusion of the boy, Gage Stevens, in a study of the drug Propulsid had also been a factor.

The manufacturer of Propulsid, Janssen Pharmaceutical Inc. of Titusville, N.J., announced last month that it would stop marketing the drug, also called cisapride, but would make it available to some patients. The company, a subsidiary of Johnson & Johnson, agreed to stop marketing the drug after consulting with the Food and Drug Administration.

Propulsid was approved for adults in 1993. It had been associated with heart rhythm abnormalities and 80 deaths, though the federal agency said it could not prove the drug caused any deaths.

The baby's parents, Scott Stevens and Gretchen Stewart of Munhall, Pa., said they had signed a **consent** form at Children's Hospital that incorrectly said the drug had been approved for infants.

In a statement released on Wednesday, officials at Children's Hospital admitted the form was wrong. They said the form stated that the drug had been approved by the F.D.A. for infants because officials believed the approval was imminent. They also said the form listed the drug's potential side effects and risks, including heart rhythm problems.

Hospital officials would not comment on the coroner's ruling.

Bonnie Stevens, the boy's grandmother, said Gage's parents did not know the risks.

"We were not aware it could cause heart problems," said Ms. Stevens, a retired registered nurse. "Who in their right mind would give it to a baby if they knew that?"

Gage, who suffered from heartburn and chronic diarrhea, had been enrolled in the study for six months when he died. He was one of 100 children participating in a **clinical trial** to determine the safety of the drug to treat gastroesophageal reflux in children. The condition is like heartburn, with stomach acid backing up into the throat.

The hospital halted the trial in March after the Food and Drug Administration told officials of a possible link between the drug and Gage's death.

Dr. Wecht said he reopened the case after being contacted by the "CBS Evening News" program and

reviewing additional information from the baby's family and the agency. CBS reported the link between Gage's death and the drug on Wednesday.

In Los Angeles, a medical center that serves primarily poor neighborhoods has halted hundreds of clinical research studies after federal investigators found more than 24 violations of rules designed to protect patients.

The Charles R. Drew University of Medicine and Science and its affiliated county-run health center, Martin Luther King Jr. Hospital, suspended the research two weeks ago, The Los Angeles Times reported today.

"No subject has ever had an adverse effect" from research at the medical center, said Dr. Tony Strickland, associate dean of research.

The university's voluntary action will affect 250 studies, some involving drugs, though hospital officials could not determine how many **human subjects** took part in the projects. About 20 studies will continue because stopping them could harm patients, the university said.

Inspectors with the Federal Office for Protection from Research Risks found this month that projects at the King center were not reviewed by an internal committee -- considered a "major violation."

Other violations included a lack of required guidelines at the medical center for conducting research on vulnerable subjects, such as prisoners and children. Forms given to patients also were not translated into Spanish, the native language of many in the area.

<http://www.nytimes.com>

LANGUAGE: ENGLISH

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