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SCIENCE IN SOCIETY:

Cloning Plan Spawns Ethics Debate

David Kestenbaum

He seemed an unlikely "man of the hour," as ABC anchor Ted Koppel referred to him in a *Nightline* interview last week. But when a gangly 69-year-old physicist named Richard Seed aired his plans to launch a human cloning clinic in Chicago, he became an overnight sensation. Seed, who is unaffiliated with any university or research institution, has told reporters that a hand-picked team of physicians will attempt in the next few months to use newly developed cloning techniques to enable an infertile couple to have a child. In the face of nearly universal unease with the prospect of human cloning, the brazen pronouncement has fired debates over the ethics of cloning--and the dynamics of science journalism, too.

Many scientists view human cloning as a tantalizing, if distant, prospect for helping infertile couples have children. It's possible "that some cloninglike technology will be the only therapy that will allow an infertile couple to have a genetically related child," says Sean Tipton, a spokesperson for the American Society of Reproductive Medicine. But given that nobody has been able to reproduce the feat that resulted in Dolly the sheep--cloning an animal from an adult cell--many experts are skeptical that what Seed has set out to do can even be done. And even if it were feasible, "the chance of abnormal offspring is high," says Roger Pedersen, a physician at the University of California, San Francisco, and a major proponent of a voluntary moratorium on human cloning that many scientific groups have pledged to adhere to.

Still, Seed's face, voice, and words were a big hit for news organizations worldwide. He has declined to disclose the names of the four couples who he said have volunteered or of the physicians he said have agreed to work on the project. But Seed, who received a Ph.D. in physics from Harvard in 1953, has not skimped on rhetoric: He told National Public Radio (NPR) that "cloning and the reprogramming of DNA are the first serious steps in becoming one with God." This and similarly eyebrow-raising statements--he even offered to clone ABC's Koppel--have drawn deep skepticism from the scientific community. "This guy should have been ignored," says Dorothy Nelkin, a sociologist at New York University. Seed could not be reached for comment.

Indeed, at first, Seed's plans were mostly ignored. Seed announced his intentions last month at a conference in Chicago on science and law, but only the *Milwaukee Journal Sentinel* and a few other regional papers covered the story; he also got a mention in a commentary in this month's issue of *Nature Biotechnology*. "I wasn't convinced he had the resources or the people to do it," says Rick Weiss, a science writer at *The Washington Post* who was at the conference but decided to lay off the story. "I didn't want to just give him a free pulpit to [raise] his venture capital."

The media snowball began rolling after NPR sent out press releases touting a story on Seed on its 6 January evening news show, *All Things Considered*. Joe Palca, who reported the story, says he was skeptical initially until Seed took him to meet some of the physicians he had lined up for the project. Palca says he hoped his story would raise public consciousness about human cloning. Many news organizations, including *The Washington Post*, felt compelled to follow NPR's lead. "I didn't want to get

scooped on a story I had known about for a month," says Weiss. Ronald Kotulak, a science writer at the *Chicago Tribune*, decided reluctantly that the newspaper couldn't ignore what had become "a national sensation." The *Tribune* put a half-dozen reporters on the story.

Even the White House jumped into the fray. In his Saturday radio address on 10 January, President Bill Clinton reiterated his determination to pass legislation that would place a 5-year moratorium on human cloning research. Ironically, some opponents of human cloning in Congress may benefit from Seed's announcement: It "certainly could help, and definitely would not harm, my efforts" to get legislation passed to ban cloning, Representative Vernon Ehlers (R-MI) told *Science*.

What worries some observers is that a rush to judgment could torpedo nonhuman cloning efforts. "Hastily drafted legislation," warns Carl Feldbaum, president of the Biotechnology Industry Organization, a Washington, D.C.-based lobby, could "inadvertently ban legitimate research" on topics such as the regeneration of nerve tissue or skin for burn victims. It's a shame, Nelkin adds, that the episode hasn't seeded a more worthwhile discussion about the risks and benefits of cloning.

Volume 279, Number 5349 Issue of 16 January 1998, p 315

January 19, 1998

Small Spark Reignites Debate on Human Cloning

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- Physicist Announces Plans for Clinic to Clone Humans (Jan. 8)

By SHERYL GAY STOLBERG

WASHINGTON -- For nearly a year, Rep. Vernon Ehlers, R-Mich., has watched, frustrated, as his legislation to ban the cloning of humans remained stuck in Congress. With such pressing matters to tend to as balancing the budget and cutting taxes, his two cloning bills, he says, got "lost in the dust."

Now Ehlers thinks he has found someone who will help speed his legislation along: Dr. Richard Seed, the little-known Illinois physicist who bolted into the news this month by declaring that he intended to open a cloning clinic.

"He may be an inadvertent ally," said Ehlers, himself a former physics professor.

While most scientists and lawmakers, including Ehlers, agree that Seed has neither the expertise nor the money to make good on his promise, his pronouncements have nonetheless revived a near moribund debate.

There was a rush to outlaw human cloning last winter, amid the furor over the announcement in February that a Scottish scientist, Dr. Ian Wilmut, had cloned mammary cells from a 6-year-old ewe to produce a sheep named Dolly. But the bills, including one proposed by President Clinton, soon languished, for a variety of reasons.

Above all, there was no immediate threat that scientists would -- or could -- clone a human. It had taken Wilmut 277 attempts to create Dolly, and there was a consensus that a similar effort to create people would be unworkable, and certainly unethical. Leaders of science and industry assured Congress that they had no plans to try.

"Everybody promised they would be on their best behavior," said Dr. Thomas Murray of the President's National Bioethics Advisory Commission, which recommended in June that the government impose a five-year ban on the creation of babies by cloning. "Congress may have just taken people at their word."

At the same time, serious disagreements arose over what such a law should say. At issue is whether the government should simply outlaw baby-making by cloning, as in a ban adopted by 19 European nations at a meeting in Paris last week, or prohibit certain cloning research as well, including studies involving embryos even when those embryos are not used to create people.

Either approach would surely drag the volatile issue of abortion into the cloning controversy, by reviving the divisive question of whether life begins at conception.

In addition, finding the right language for whatever ban is adopted could prove vexing. Scientists, many of whom oppose making genetic replicas of people, caution that if such a law is not carefully drafted, it could wipe out entire areas of very fruitful medical research.

For instance, the technique used by Wilmut might someday be used to produce skin tissue for burn victims, or organs for transplant. If the technique itself is outlawed, as some have proposed, those advances will be impossible.

"It's a whole new area of law," said Leanne Jerome, spokeswoman for Sen. Christopher Bond, R-Mo., who has spoken out against human-cloning research. But "we thought we were still a ways away from anyone attempting human cloning."

Enter Seed, a science entrepreneur without formal affiliation with any institution, who in a brief telephone discussion declined to make any comment except to say of cloning opponents in Congress: "They're entitled to their opinion. I'm entitled to my opinion."

Seed, branded "irresponsible, unethical, unprofessional" by the White House and a "mad scientist" by Donna Shalala, the secretary of health and human services, has managed to accomplish what months of level-headed scientific and ethics discussion could not: he has put cloning back on the political map at the very time some thought it was disappearing.

In the wake of Seed's pronouncements, both Bond and Clinton vowed to renew their efforts to ban the cloning of humans. And late Friday, Sen. Dianne Feinstein, D-Calif., announced she would introduce legislation to outlaw making babies through cloning for 10 years, a period twice as long as the president proposed.

"We need time to develop the ethical and legal structure of the use of this technology," Feinstein said Sunday. The bill, which has not yet been drafted, would make Feinstein the first Democrat in Congress to weigh in on the cloning issue.

That Seed has struck such a sensitive chord on cloning is proof to many that people reject cloning of humans as immoral.

R. Alta Charo, a member of the president's bioethics panel, says Seed is feeding the public's fear of the rogue scientist.

"Along with Dr. Frankenstein and Dr. Kevorkian," Ms. Charo said, "we now have Dr. Seed."

While Ms. Charo believes that the cloning of people should be banned while matters of safety and ethics are worked out, she worries that Seed will spawn "a

rush to legislation that could create silly obstacles to scientific research."

Lawmakers did adopt an appropriations provision last year that barred federal spending on any research that would lead to the cloning of people, and Clinton subsequently issued an executive order extending that ban indefinitely. But those measures were largely symbolic, because the government already refused to pay for research involving embryos. The trickier question is whether to impose such a ban on private-sector spending, and, if so, how.

The president's bill, which lacks sponsors, provides for a narrow ban. Following the recommendations of his bioethics commission, Clinton would prohibit only those cloning experiments that include the implanting of an embryo in a woman's womb with the intent to make a baby. The law would expire in five years, after which the issue would presumably be revisited.

Ehlers has proposed two bills. The first, which has been passed by the House Science Committee, would permanently bar federal financing of cloning studies, and the second, which has not had a hearing, would impose a similar ban on spending by the private sector. The first bill would apply to any research on embryos, and Ehlers plans to add a similar provision to the second.

"Those who are pro-life believe that a human embryo has all the characteristics of a human life," Ehlers said.

Like Ehlers, Bond hopes that the Seed announcement will breathe life into the anti-cloning offensive.

"Dr. Seed's grandstand effort makes it imperative that we now move with a ban on all human-cloning activities," Bond said, "to make it clear that no matter what the scientific capabilities are, there are certain paths down which we should not go."

Bond and Ehlers agree that any legislation adopted should outlaw embryo research, a provision that Feinstein opposes. The idea has also aroused the ire of the biotechnology industry and the American Society for Reproductive Medicine, which represents doctors engaged in the study of infertility.

Heather Kowalski, spokeswoman for the society, said the organization would present its own proposal Tuesday to ban the cloning of people.

Ms. Kowalski said imprecisely worded legislation was already affecting infertility work. In California, the only state that has adopted a ban on human cloning, the law prohibits scientists from transferring the nucleus of one human cell into another cell.

But such a procedure is not by itself considered cloning; in New York, doctors are studying it as a method for helping infertile couples conceive, but only through interaction of both sperm and egg.

Another bill, proposed in Florida but eventually withdrawn, would have outlawed the cloning of human DNA. But scientists routinely copy human genetic material to make medicines for disorders including heart disease and cancer. And DNA fingerprinting, a technique used in criminal cases across America, relies on this type of cloning.

"It was a well-intentioned bill, but it would have made felons out of researchers," said Carl B. Feldbaum, president of the Biotechnology Industry Organization, which represents 750 biotechnology companies and favors a law

against making babies through cloning.

Then there is the question of how such a law would be enforced, and what penalties it would carry.

"You certainly don't want to create a system of cloning police," Feldbaum said.

And some wonder whether a ban, even one that prohibited only baby-making through cloning, would withstand scrutiny in the courts.

"At the point at which cloning becomes possible, such a ban would be challenged," said John Robertson, a professor of law and bioethics at the University of Texas, who foresees instances where creating a baby by cloning might be ethically defensible.

Robertson said such a challenge might come from the parents of a child who is dying of leukemia who want to clone that child to create a perfect bone marrow match.

Robertson believes that anti-cloning legislation is a bad idea, and laments that Seed "is probably going to get the legislation passed that otherwise would have died."

But Murray, the bioethicist, says Seed may be a blessing in disguise.

"If his meteoric rise on the American scene, which I think will be followed by an equally meteoric fall, will have prompted Congress to pay attention to human cloning," Murray said, "that would be a good consequence of an otherwise noisome controversy."

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Cloning Without Human Clones
By Meredith Wadman

01/20/98
The Wall Street Journal
Page A18

Maverick Chicago physicist Richard Seed received a great deal of attention recently when he announced plans to produce a human baby by **cloning** within the next two years. Over the weekend, University of Wisconsin scientists reported that they had successfully cloned five species -- including primates -- using cows' eggs as "incubators"; all resulted in miscarriages. The procedure, if ever perfected, could be another tool for the likes of Mr. Seed: If you can clone monkeys from a cow's eggs -- which are far more readily available than human ova -- why not human beings?

These developments will only increase the pressure already building on Congress to stop all human **cloning** as soon as it reconvenes next week. And Congress should act: Even if an experiment like Mr. Seed's is one day successful -- and the physical risks are now grave -- there are significant unresolved moral and ethical questions surrounding the creation of a human who is the genetic duplicate of another. But Congress should be careful to go after **cloning** with a surgeon's scalpel, and not a chain saw. Otherwise, the politicians risk stifling highly promising medical advances, from improved repairs of battered organs to better infertility treatments that don't involve duplication of any adult.

The states are already learning the perils of careless **cloning** bans. Last spring in Florida, a bill introduced and then swiftly withdrawn would have banned the **cloning** not only of people, but of DNA -- virtually destroying that state's biotechnology industry. California lawmakers, in the rush to get out of Sacramento last September, passed a **cloning** ban that also outlawed oocyte nuclear transfer, a promising potential treatment for infertile mothers. This procedure, pioneered by New York University's John Zhang and Jamie A. Grifo, would produce ordinary children, not clones.

Infertility isn't the only malady for which **cloning** technology shows promise. The **cloning** experiment that created the famous lamb Dolly opened up remarkable prospects in the area of repairing devastated tissues and organs, because it proved that an adult cell that has become specialized to do a particular job -- say, to be liver or blood -- can "unlearn" its role and be reprogrammed to do something quite different.

The applications are breathtaking. Imagine a day when a patient with

severe liver disease might see another cell of his body -- skin, hair, whatever -- reprogrammed to act as a healthy liver cell, without the risk of immune rejection inherent in receiving a donated liver. Or a cancer patient whose bone marrow has been wiped out by radiation could be treated with bone marrow grown from another cell of his own body.

To get from here to there, scientists will need to use **cloning** techniques to study the biological processes at work in days-old embryos. They need to answer questions such as how the DNA and its cellular surroundings interact in the early embryo to direct cells to take their very first steps toward ultimately becoming, say, liver or blood cells.

Much of this work can now be done in animals, but not all. And with time, if human treatments are sought, work will need to be done with human embryos. These are microscopic clusters of eight to 100 cells -- embryos confined to petri dishes, not bound for baby buggies.

Congress each year bans federal funding for such work. But this research is legal if financed privately. The worry among scientists is that Congress, when it considers banning **cloning** for baby making, will not be able to resist banning its use in private embryo research as well.

Indeed, that tendency showed up in the House last summer. Rep. Vernon Ehlers (R., Mich.), a physicist by training, was forced by Science Committee colleagues to rewrite a bill banning federal funding for the **cloning** of babies to extend the ban to **cloning** 's use in embryo research. The committee passed the bill, which has since languished.

Physicians and scientists were not pleased. "We are very worried that this bill . . . has become a permanent embryo research ban," Sean Tipton of the American Society for Reproductive Medicine said at the time.

This group -- composed mainly of infertility doctors -- isn't alone. Harold Varmus, director of the National Institutes of Health, told Congress last March: "When I hear about research on human **cloning** as something that ought to be taken away, I shiver." The great majority of scientific societies responding last year to a poll by a presidential bioethics commission said that they opposed restricting the use of **cloning** technology for basic developmental-biology research, or for making specific human cell types. Trying to protect that research, scientists are backing the approach President Clinton took in a bill he sent to Congress last June. It would ban **cloning** for baby making, and not meddle with research.

Honorable people certainly can differ on the ethics of embryo research. So far, Congress has held off banning such work when it's not financed by taxpayers. When the politicians take up **cloning** , they will serve the public best if they show similar restraint.

Dr. Wadman covers biomedical research policy for the British journal

Nature.

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STRANGE EGG

A house call to the mysterious Doctor Seed, the man who wants to clone humans.

By Gene Weingarten
Washington Post Staff Writer
Sunday, January 25, 1998; Page F01

RIVERSIDE, Ill.— RIVERSIDE, Ill.—He is brilliant. He is broke. He is a prophet. A fruitcake. A flop. He is the most famous scientist on Earth. But he hasn't been taking phone calls for days, so you just show up at his door.

From outside, you can hear the phone ringing and ringing, so you guess no one is home. Then the door opens and there he is. A dangerous man, it is said. He has been denounced by the president of the United States, castigated by the secretary of health and human services, threatened by the Food and Drug Administration. Congressmen want to pass a law to prevent him from doing the terrible thing he wants to do.

He blinks, befuddled. His trousers do not match his jacket. His lapel bears a juicy stain. You are not the Fed Ex man?

No.

Confound it. He should not have answered the door.

Behind him the phone keeps ringing. He doesn't bother with it anymore, he explains. Too many reporters, calling from too many places. The last one was Bogota. Some people have left messages offering oodles of money, he says. He'll get back to them when he can. He's afraid the answering machine tape has run out. Confound it.

Distractedly, he waves you to a seat. The furniture is old, the fabric shiny. He walks with an old man's stoop and shuffle. His great, gaunt body is adrift in his clothes, his pants hanging loosely from clip-on suspenders. His face is fissured, his eyes haunted, his mouth set in a thin, wry grin.

What does the scientist want? Fame? Riches? Eternal life?

Yes, yes and yes. This last one in particular intrigues him.

"There is a powerful urge to live," he says. "The urge to die is negligible. If you did not have the urge to propagate, the species would not survive."

One way to live forever is to get married, and copulate, and have children, he says. He has had three wives, seven children. Copulate,

and procreate.

But soon, he says, his voice rising to a thundering rumble, "there will be another way."

This is Richard Seed, 69, the bearded, grumpy, Bible-thumping, Harvard-educated physicist and fertility researcher who says he is going to open a human cloning clinic for childless couples. He estimates he is about $2 million and two years away from the first birth. He claims to have assembled a medical team. Four clients, he says, are on standby.

His announcement, made last month at a Chicago symposium on reproduction, exploded like heavy ordnance, with a bang and a shudder. To many, the prospect of human cloning -- creating an embryo by duplicating the genetic material of one person -- is profoundly troubling; it creates life without love or physical communion, a narcissistic intrusion into the work of God. But until Seed came along, it had all seemed comfortably theoretical. When scientist Ian Wilmut produced a healthy cloned sheep last year in Scotland, President Clinton and some bioethicists pushed for a national ban on human cloning. They found little enthusiasm; it was a complex issue, it seemed remote, and the scientific community was not of one mind.

Then, suddenly, the danger had a face. It was a scary face. Forbidding. Mephistophelean. Its eyes smoldered. When it spoke, it growled.

For those who would want to demonize human cloning, this was too good to be true.

The demon Seed.

He was defiant. He was rude. When the president said he would move to prevent the cloning of humans, Seed responded that he would simply move his operation to Tijuana, Mexico. When Clinton suggested, through a spokesman, that Seed was irresponsible and unethical, the physicist said of the president, "As far as I am concerned, he's slick, sleazy Willy."

Overnight, it seemed, efforts to outlaw human cloning picked up support. The rhetoric intensified. House Majority Leader Dick Armey (R-Tex.) decried the prospect of "a Brave New World of sidewalk cloning clinics." A member of the president's bioethics commission likened Dr. Seed to two other doctors: Kevorkian and Frankenstein. The ramifications of human cloning were examined ad nauseam in the national media, down to the specter of genetically manipulated, headless human fetuses being farmed for their organs.

Meanwhile, people who knew Seed were plainly mystified.

"He's nuts!" says Dick Seed, 37, a graphic designer from Truro, Mass. Dick is Richard's son.

"He's nuts, but he's creative," said Robert Seed, 23, a computer programmer in Chicago. Robert is also Richard's son.

"You can imagine my amusement when I saw the president of the United States responding to this person," says Mary Walters, laughing. "I felt like I was in the Twilight Zone."

Walters was Richard Seed's next-door neighbor for 10 years in the stately Oak Park, Ill., historic district, a neighborhood famous for its Frank Lloyd Wright architecture. The house Seed and his wife lived in stands vacant these days, dark and windswept. The new owner appears to be gutting it, "thank goodness," says Walters.

Seed lost it to foreclosure last summer, after living there 12 years with his third wife, Gloria. Once comfortably well off, he says he is "out of money."

"Bad investments," he says, pacing the living room of the small house he lives in now in this Chicago suburb. He consults his watch. He's a busy man with many important appointments. How long will this take?

This is not about his personal life anyway, he says sourly. What does his personal life have to do with whether he can pull this cloning thing off?

Human cloning is inevitable, he says.

"If not me, then someone else. If not here, then somewhere else. If not now, then."

Seed talks like that, with grand flourishes and hints of mystery. He will not disclose the names of his partners in this venture, not the nurse, not the embryologist, and certainly not the obstetrician-gynecologist, a man he calls "my obie-gynie."

"If I did," he says, noting the furor that swirls around him, "his business would be ruined."

"Neither of us likes to lie, but I have told him to lie, to deny any connection with me if he is asked."

So there is no way of confirming that he has any allies at all?

"Correct."

The Seeds of Oak Park are an intellectual and accomplished family. Richard Seed is the son of a prominent Chicago surgeon who, in the 1930s, helped pioneer blood banking. Seed's brother Randolph is a doctor, and so is his brother John. Richard went into physics, earned three degrees at Harvard, and all his life teetered on the brink of spectacular success, only to fall into an abyss. He may have had the scientific skills of a Fermi, and the entrepreneurial instincts of a Carnegie, but he also had the attention span of a toddler.

In the 1950s, he began a semiconductor business in his basement. Few people had then heard of semiconductors, which would become the infrastructure of the computer industry. Seed left the company shortly before people made vast fortunes in semiconductors.

Then he was into gas lasers. Same thing.

"He has a problem with follow-through. He has no sense of closure," says his son Russell, 34, who lives in the Chicago area and once was in the mortgage business with his father until they had a falling-out. Richard was lousy at the mortgage business, says his son. The mortgage business, says Russell, "is about pushing papers from one side of the desk to another. It is not intellectual. There is no fun." Richard got bored and careless, Russell says. He lost his money.

Seed was famous once before. In the 1970s, with his brother Randolph, he ran Embryo Transplant Corp., which developed advanced reproductive techniques to produce high-yield milk cows. Seed figured out a non-surgical procedure to super-ovulate the most productive cows, and then wash the embryos out of the uterus to be implanted in other cows. From one "super cow," as many as 12 super calves could be born. It was an ingenious idea, and it worked, but Seed's company went bust because it depended on the financial health of the farming industry at a time when agribusiness was in trouble.

"We weren't too sharp, business-wise," Randolph once told the Associated Press.

Seed was undeterred: He figured the egg-washing procedure would work on humans. A doctor would remove an embryo from a fertile donor and transfer it to an infertile woman client, who would carry the baby. No surgery would be necessary. Working with his brother Randolph, he got funding in a public stock offering and formed Fertility & Genetics Research Inc. in 1979.

It got national publicity. Seed predicted 50,000 procedures a year, thousands of bouncing babies. Instead, there were three. The technique proved more difficult than Seed had anticipated. "There were technical problems," he says. Eggs didn't wash as easily out of humans as they did out of cows. In vitro fertilization -- the surgical procedure that produced the world's first test-tube baby in 1978 -- became the state of the art.

Fertility & Genetics Research went belly up. Next, Seed showed up one day in the late 1980s in the office of Walter Cornett, a venture capitalist in Glenview, Ill. The first thing Seed told Cornett was that he, Seed, was "the smartest man in the world." The second thing he said was that he had a secret plan to corner the world's market on fish meal. All he needed was $35 million.

"I thought he was a couple of bubbles off plumb," Cornett says.

Cornett listened, though. Seed had done his homework. He had been studying menhaden, an East Coast trash fish harvested for its oil. After the oil was extracted, the rest of the fish was ground up and sold cheaply for fish-meal fertilizer and animal feed. Seed had learned that there were only seven small, struggling fishing fleets that caught all of the menhaden, and he proposed secretly buying up them all, and then bumping fish-meal prices through the roof.

Cornett didn't nibble. He didn't have the money.

"You know," he says today, "it was not a farfetched idea. It might have worked."

But Seed never pursued it. Instead, he went into mortgage banking with his son. Lost his shirt.

By and large, the scientific community has been contemptuously dismissive of Richard Seed, a research scientist who has gone 10 years without a significant research project. The consensus seems to be that human cloning may someday be possible, that it may indeed be inevitable, but that Seed will not be the man to do it, that he lacks the scientific rigor.

Seed is amused that everyone says cloning humans will be fraught with peril. Humans are much easier to clone than sheep or cows, he contends.

The refinement of in vitro fertilization techniques, he says, has made human cloning a relatively safe and simple procedure. Ultrasound probes into the vagina make the extraction and implantation of eggs simple and accurate, he says.

What about the possibility of error in human cloning? Ian Wilmut had 276 failures before Dolly the sheep was born. Some of them were grotesque. Fetuses grew monstrously large. Fetuses were deformed. Fetuses had to be discarded. Wilmut has said he would anticipate similar problems with humans.

He's wrong, says Seed.

"My solution is DNA fingerprinting before transfer." He explains: The same technique used by forensic scientists to catch criminals can be used to make sure that the genetic material of the donor and the clone are identical. "You look at those long pages of dots and make sure they are identical. If the clone dots are identical to the donor dots, it is impossible to have chromosomal abnormalities."

Can it possibly be that simple?

He smiles. "Maybe these guys haven't thought of it yet."

The phone keeps ringing. Seed keeps peevishly checking his watch. Appointments await.

"You are clearly not as intelligent as I am, you recognize that, don't you?"

This comes out of nowhere. Is he joking?

"You don't think as fast as I do."

He is not joking.

"You don't use words as large as I do."

The doctor does not lack for self-esteem.

"I am a near genius," he says, and then corrects himself. "I am a former near genius."

A former near genius?

He does not elaborate.

The doorbell rings. Seed rises to answer it.

"Doctor, I have seen you on TV and I have great respect for the work you are doing." Seed tut-tuts his thanks. There is a shuffle of papers.

"I am Anthony . . . and I have something I would like you to read."

Anthony is small and pudgy and earnest. He proffers a document.

"The federal government is illegally using microscopic technology on me," he says. "They made me consume something that can communicate to your neurons with electrical impulses. The federal government is committing this crime against me. I am having problems getting this recognized by the state police because it makes people look like they are mentally ill. It mimics schizophrenia, and I am hoping you can help me."

Seed graciously agrees to look at the material.

When Anthony is gone, Seed smiles sadly and spins a finger in circles against his temple. There are many things about which he is cynical, and he is contemptuous of people who he feels are of inferior intellect, but he is not making fun of the visitor at the door.

"I try to be polite. There is nothing to be gained by hurting people's feelings."

He knows what it is like to be called a madman.

Seed has some secrets. As the hours pass, he dribbles them out. The first is his "secret number." It is 200,000, and it is what he predicts is the total yearly market for human clones in the United States. The infertility market, he says, is relatively small, only 3,000 sterile couples a year. Where will the other 197,000 customers come from?

"People with strong egos, who want to clone themselves."

People like Richard Seed?

"Yes."

Will he clone himself?

"Yes."

A second secret appears to involve payment of a gratuity to a sovereign state. Richard Seed says that if he is forced to go to Mexico, his start-up costs will rise from $2 million to about $2.5 million.

"I don't disapprove of bribes," he says matter-of-factly. "We cannot impose our standards of behavior on a more primitive part of the world."

He says he would also set up a free medical clinic in a poor part of Tijuana "to buy goodwill. Then they'd have a hard time tossing me out of town."

He leans back in his chair, then sits bolt upright. "Hey, what if I put up a free medical clinic in the Chicago Housing Authority? This is worth thinking about!" He makes a mental note.

The phone keeps ringing, unanswered.

Seed's third secret is a secret fantasy. He envisions a cure for cancer through cloning.

The nuclei of breast cancer cells, he says, look normal in the early stages of the disease, and later get deformed. He proposes taking new cancer cells, in this early stage of development, and putting their nuclei in other cells. You let them divide and grow -- essentially the same process as cloning -- and see if you get something without cancer.

"Then you will have reprogrammed the cell from a cancerous state to a noncancerous state," he says. "You would not have cured this cancer, you would have cured all cancer."

But what will you have created? What if you get something grotesque?

"A lumpy beast?" Seed asks, laughing.

Yes. A monster.

"Well, if it is a lumpy beast without cancer, you are still 90 percent of the way there! It would be astonishing, biologically."

But what would you do with the monster?

"I'd freeze and store it," he says.

See? No problem.

Seed is dismissive of most ethical objections to cloning. He gives an example:

His clinic is going to serve infertile couples. Because a clone is the genetic copy of one person only, the first baby born to a client would be a genetic duplicate of either the father or the mother. Then the couple would come back, a year or two later, and duplicate the other parent.

So now they would have two children, one boy and one girl.

These children would grow up as brother and sister in the same

household, but they would have no genetic material in common. They would be little genetic duplicates of their father and mother.

Now, what if they fell in love, just as their father and mother did? What if they married?

"Some people think that would be horrible," Seed says. "I don't see anything wrong with it." You have to be a scientist, he says. You have to define incest genetically.

"I have a feeling clones won't marry, though. Brothers and sisters don't like each other, you know. If you want them to fall in love, you would have to send them to separate boarding schools. It would be interesting to see, though I don't think it would be a problem no matter how it comes out.

"Actually, I don't like boarding schools. I don't approve of sending your children away."

There are seven Seed children, five men and two women with three different mothers. They are scattered across the country.

"He's stimulating," says Russell of his father. "He is a loving, caring father, but he is not very good at expressing that. Not many of his children are as close to him as I am, and I am not very close to him."

Says son Robert: "Me and him, when we talk, we pretty much only talk about science."

Seed admits he can seem cold and clinical. Not to mention insufferable. "Can you imagine listening to me 24 hours a day?" Sometimes, he says, his wife will go to the bathroom just to get away from his hectoring.

"I'll follow her in, because I wasn't finished."

It is evidently impossible to live with Richard Seed and not be exasperated with him, and impressed by him in spite of yourself.

Robert Seed believes his father can clone humans. So does Russell Seed. So does Dick Seed, even though he has seen his father only a few times in the past 25 years. Richard left when he was 10.

And so does Zaroohy Seed, Richard Seed's second wife. They were were married in 1960, divorced in 1972.

Zaroohy calls her ex-husband "dynamic, ambitious and interesting." Also completely maddening.

What does he want?

"Money," she says. He gets money, then excretes it "right down the toilet."

That's it? Money?

Money first, she says, then scientific challenge and, finally,

immortality.

"He once wanted to be preserved cryogenically, can you believe that? I would have pulled the plug."

The former Mrs. Richard Seed pauses to let this sink in.

"I'd have not paid the electric bill, and quietly let the lights go off. And that would be that."

In his living room, Richard Seed is pondering immortality. Cloning, he is convinced, is part of God's plan. Beside his chair is the Good News Bible, a modern translation of Scripture. Seed is a devout Methodist.

"In the first two chapters of the Old Testament, we learned that God made man in his own image. He intended the union of man and God. Is this union spiritual or in body? I think it is talking about the body. That we would become God in body and spirit."

Cloning is the first step, Seed says. The second step is manipulation of the genetic material to reset the human body clock, to end the aging of cells. "Indefinite life extension," he calls it. Man becomes God.

But for the moment, he will have to be content with more conventional avenues of immortality. Copulation. Procreation. Family. The immortality that comes with memory.

Seed's living room is sparsely furnished. By far the most imposing feature is a pair of lighted display cases, 7 feet tall, 3 feet wide. They are filled, top to bottom, with earrings. There are perhaps 800 pairs of earrings, row upon row, neatly arranged, hanging from bars. Some are delicate, some are ungainly, some are expensive, but most seem like costume items, plain and cheap. This is not a particularly valuable collection, except to Richard Seed. They were his mother's earrings. It is her shrine.

"See that beautiful woman?" he says, pointing to a framed portrait amid the earrings, hand-tinted in the manner of the 1930s. Frances Seed was indeed an elegant woman.

"My mother was a minor socialite and a lady -- you never heard her say a foul word in her entire life," Seed says. "She was a very interesting woman. She never struck us. Maybe a tap on the hand.

"My mother didn't know us," he continues, his voice softening. "My brother and I spent our childhood torturing each other, chasing each other. We would jump out the window, jump off the second floor! She didn't know who we were. She thought we were just ruffians who tore through the house.

"My father was the last of the Victorians. He was very proper. He would never use an improper word. He was a good father, but he had no demonstrable affection for his children. We used to drive him nuts. One of my favorite games was to sneak up behind him when he was reading the Sunday paper, like a lion cub, and bat the paper out of his hands. It is a very startling thing when that happens. . . .

"I never saw my father ill, and then he up and died of prostate cancer."

Seed has prostate problems himself.

He trails off.

"I had an almost idyllic childhood," he says.

And then life got very, very complicated.

"I am disappointed at my achievements," he says. "God gave me a lot of ability and I don't have all that much to show for it. He gave me creative and inventive abilities. Robert Noyce was at MIT when I was at Harvard. He's the inventor of the integrated circuit. I consider myself more competent than Noyce. But he made an enormous contribution, and I haven't."

Above all, he says, he regrets not winning a Nobel Prize. He always wanted to win one, and now, he says, it is too late.

Too late?

"You lose a lot of brain cells as you get older," he says. He is not complaining, he is speaking clinically, like a scientist.

This would explain why he is a former near genius?

"Right," he says.

"You get dumber and dumber," he says. "Your body gets weaker and weaker, too. But that is not as frightening."

The public unraveling of Richard Seed began shortly after he burst into public view this month. A series of articles in the Chicago Tribune revealed his financial troubles, his unsuccessful business schemes, his grandiose posturings. The Tribune also spoke of an old criminal charge against Seed, something from 1990 allegedly involving medical malpractice. The newspaper did not obtain the records, and Seed would not discuss it. His silence seemed damning. He said he was protecting someone who would be hurt by the disclosure. To the cynic, that someone seemed to be Seed himself.

To this day, Seed has continued to refuse to talk about this incident.

The records are in the Chicago criminal courts. This was one of the few things the Tribune got wrong. The case had nothing to do with malpractice. People involved remember it well.

On July 19, 1990, Richard Seed and his wife, Gloria, brought their younger daughter to a private hospital. She was 14 or 15. She was distraught. She was threatening suicide. A hospital psychiatrist ordered her held for observation and treatment, against her parents' wishes. They wanted to take her home. Instead, an ambulance arrived to transport the girl to a state mental facility, apparently because the Seeds were uninsured.

Not only was she not going home, she was being sent to a place not known for the quality of its care, a facility that Seed considered a snake pit.

He tried to place himself between the ambulance and his daughter.

There were shouts, and a scuffle. Seed was arrested and charged with disorderly conduct. Eventually the case was dismissed. The daughter was treated and released. She is 21 now, and doing okay.

One hospital employee who was at the scene remembers a tall, dignified man, welldressed, half crazy with fear and humiliation, fiercely fighting to protect his child.

"I could understand why he did it. I could definitely understand. I might have done the same thing."

Because he understands genetics, Richard Seed is confident he's got maybe a quarter-century left in him. He has the genes for long life. His mom -- the earring lady -- died in her nineties.

Before he dies, he expects to be cloned, but, he says, that will not be immortality: "It won't be me." He's right, of course. It won't be Richard Seed. It will be a baby boy who will grow up to be a whole lot like him. Ingenious. Arrogant. Impulsive. Obstinate. Irascible. Eccentric. Immature. Decent. Loving. Distant. Kind of sweet. Kind of sad.

But truth to tell, it probably won't happen. Few people other than Seed figure humans will be cloned that soon. The government is doing everything it can to see that he doesn't move forward. The Food and Drug Administration last week announced it would have to license any procedure involving human cloning. Presumably, the approval process would take years and years.

So Richard Seed probably will die unduplicated, and, like the rest of us, he will probably live on the way we all live on. He will have to rely on the old system.

Seed is asked what he would most like out of life, now that the Nobel is beyond his reach. Does he want to be wealthy? Respected? Vindicated?

Nothing he has said in the previous four hours prepares you for his answer.

"I would like all of my children to go to my funeral."

That is all?

"I would like them to say, 'He was my father, and I loved him.' "

For once, Richard Seed's composure breaks. The most dangerous scientist on Earth wipes away a tear.

Article 1 of 1
Editorial Desk; Section A
Why The Rush To Ban Cloning ?
By Arthur L. Caplan

01/28/98
The New York Times
Page 25, Column 2

PHILADELPHIA -- Richard Seed, the retired physicist who scared the nation to death earlier this month with his talk of creating a brave new biological world, has inadvertently become the poster boy for regulating cloning. It does not seem to matter that Dr. Seed, who has none of the laboratories, technical skills, money or other tools requisite to harness this powerful and dangerous technology, will never clone anyone.

Regulation is all but an inevitability. This situation should make people like me, who think human cloning should proceed at a snail's pace, ecstatic. But I am not ecstatic. Before the President, Congress, the Food and Drug Administration or anyone else rushes to ban anything, we need to be sure that laws and regulations do not control human cloning at the cost of forgoing the huge benefits that animal and cell cloning will bring.

If cloning can be perfected, which is by no means a certainty, it will permit the easier mass production of animals with particular traits. The same will be true for cells and many types of tissues. That means more food at less cost, a cornucopia of biologically valuable substances available in huge quantities, and the ability to preserve species on the verge of extinction.

The benefits of rushing to attempt human cloning are far harder to see. So it is clear what the goal of regulation and legislation ought to be: to buy us the time to insure the safety and proper oversight of human cloning work. Put a moratorium of a few years on any effort to create a human being by means of cloning.

But therein lies the problem. Can legislation be written with the requisite precision? The early signs are not good. The torrent of legislative and regulatory ideas now being floated are not limited to human cloning. Most troubling, some legislators are tempted to use anti-cloning measures to try to ban or limit abortion and embryo research.

The latest to offer a regulatory response to the cloning question is the F.D.A. The agency says anyone who wants to clone will have to answer to it.

What is not at all clear, however, is whether a regulatory body

charged with insuring the safety of drugs and medical devices intended for commercial sale has the standing to say anything about human cloning. Nor is it clear from the agency's statements what the F.D.A. thinks its authority and enforcement powers are. Even if the regulatory net of the F.D.A. is extended to human cloning, the way to debate the pros and cons and fine points of the subject is not through the filter of a bureaucracy whose mandate does not include metaphysics.

Some state legislators are also getting into the act. In Minnesota, Alabama and many other states, bills are pending that would ban or limit cloning, and California has already imposed a ban. But cloning is not an activity that should be handled at the state level, since having 50 sets of rules would make little sense. Moreover, such local efforts -- which have included proposals to ban all forms of cloning, to make any manipulation of human embryos illegal and to ban any use of human genes in genetic engineering -- are a cure far worse than the disease.

In Congress, pro-life forces are eager to use anti-cloning legislation to outlaw abortion, fetal tissue research and embryo research. When Representative Vernon Ehlers, a Michigan Republican, introduced a bill in the House last year to ban Federal financing for human cloning, he soon found himself hauling around a proposal that banned human embryo research as well. If human cloning becomes just another pawn in the ongoing abortion wars, we risk living with a law that covers too much for reasons having nothing to do with cloning. Or we risk having no legislation at all.

What we need is a political agreement to keep the focus squarely on human cloning. Talk of outright bans should stop. Efforts at regulating cloning at the state level should cease. Regulatory agencies should stand aside and let the American people ask for a breather through Federal legislation.

A moratorium would give us the time we need to decide where to go next when and if cloning technology has been shown safe and reliable in animals. We should not let the likes of a Dr. Seed or abortion politics make us do anything that will make the benefits of cloning impossible to obtain.

Drawing (MK Mabry)

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January 29, 1998

FDA'S EXISTING STATUTORY AND REGULATORY AUTHORITY GIVE THE AGENCY THE BROAD AUTHORITY TO REGULATE THE CELLULAR MATERIALS INVOLVED IN HUMAN CLONING

I. Executive Summary

The Food and Drug Administration ("FDA") presently has clear and far-reaching authority to regulate potential future efforts to clone human beings, including efforts of the type suggested by physicist Richard Seed.

The cellular materials that could be used in the human cloning process 1/ are biological products fully subject to the investigational and premarket approval requirements of section 351 of the Public Health Service Act ("PHS Act"), 42 U.S.C. § 262 *et seq.* Any medical devices or drugs utilized in this process would be subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 201 *et seq.* Even experiments in a non-clinical setting of a purely investigational, non-commercial nature would be subject to FDA regulation under Section 361 of the PHS Act, which provides broad discretion to FDA to enact regulations necessary to prevent the spread of communicable disease. (This provision serves as the basis of FDA's regulation of human tissue intended for transplantation.)

1/ These cellular materials would include the donor cell and nucleus and recipient cell and nucleus involved in human cloning activities (the "Cellular Materials").

In 1993 and 1997, FDA issued guidance documents underscoring for the public that materials that are the same as or similar to the Cellular Materials discussed below are subject to the PHS Act and the FD&C Act. FDA has applied these laws consistently with the 1993 and 1997 guidance documents.

FDA has historically taken the broad public health authority granted to it by the PHS Act and has developed its policies in an evolutionary way to address rapidly advancing scientific knowledge. Courts historically have granted FDA great deference in exercising this authority.

In conclusion, FDA presently has broad statutory and regulatory authority to assert jurisdiction over the Cellular Materials involved in future human cloning experiments. That jurisdiction exists whether the experiments are commercial or non-commercial. Such an assertion of jurisdiction is consistent with FDA's previous activity and stated policies on cellular materials.

II. Background on the Science of Cloning

The application to humans of cloning procedures recently described in the scientific literature would involve cellular materials similar to those currently regulated by FDA under its existing statutory and regulatory authority. Although apparently difficult to accomplish, the cloning process reported is relatively straightforward. 2/

2/ The historical development of the technique is described in *Cloning Human Beings*, Report and Recommendations of the National Bioethics Advisory Commission (June 1997) at 13-22.

The process described by Wilmut *et al.* involves extracting the nucleus from a somatic cell 3/ of an adult and transferring it to a reproductive cell (from a different animal) whose own nucleus has been removed or inactivated. 4/ Insertion of the donor cell into the recipient cell may be accomplished directly by injection, as in previous cloning experiments, or by placing the donor nucleus and recipient cell side by side and applying a small burst of electricity to induce fusion of the two ("nuclear transfer"). Importantly, the electrical burst also initiates cell division ("activation") of the fused cell, which otherwise may not occur. Following successful nuclear transfer and activation, the product (a dividing cell with a donor nucleus) is "artificially inseminated into a surrogate [mother]." 5/

III. FDA's Existing Statutory and Regulatory Authority Provide the Agency with the Discretion to Regulate the Cellular Materials Used in Human Cloning

As set forth below, FDA currently possesses broad statutory authority under the FD&C Act and the PHS Act to regulate products intended to cure, treat, prevent, or diagnose diseases or other conditions affecting human beings. Although many of the modern biotechnology products available today were not contemplated at

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3/ "Somatic cells" are all cells other than sperm or ova; "germ cells" denote sperm or ova. *Id.* at Appendix A (Glossary).

4/ I. Wilmut, A.E. Schnieke, J. McWhir, A.J. Kind, and K.H.S. Campbell, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," 385 *Nature* 810 (February 27, 1997) (hereinafter, "Wilmut *et al.*").

5/ Ehsan Masood, "Cloning Technique 'Reveals a Loophole,'" 385 *Nature* 757 (February 27, 1997).

the time the relevant statutes were drafted, Congress ensured that the applicable FDA statutory language is broad enough to encompass the products of the rapidly evolving field of biotechnology. Accordingly, the existing statutory and regulatory authority, which are described below, provide FDA with complete authority to regulate the Cellular Materials that would be involved in human cloning.

A. FDA Has the Statutory Authority to Regulate Human Cloning Under Section 351 of the PHS Act

Under section 351 of the PHS Act, FDA is authorized to regulate biological products introduced into interstate commerce. 42 U.S.C. § 262(a). The recently enacted Food and Drug Administration Modernization Act of 1997 ("the Modernization Act"), Pub. L. No. 105-115, § 123, 111 Stat. 2296, 2323 (1997), defines a "biological product" to mean "a virus, therapeutic serum, toxin, antitoxin, vaccine, *blood, blood component or derivative, allergenic product, or analogous product,* or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), *applicable to the prevention, treatment, or cure of a disease or condition of human beings.*" PHS Act § 351(i), 42 U.S.C. § 262(i) (emphasis added). This definition includes cellular products, such as somatic cell products, which are considered to be "analogous" to blood, blood components or derivatives if they are used for the prevention, treatment, or cure of a disease or condition of human beings. Cellular products that currently are regulated by FDA as biological products include: (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 when such products are used for the prevention, treatment, or cure of a disease or condition of human beings. 58 Fed. Reg. at 53250.

Section 351 of the PHS Act requires that prior to moving in interstate commerce a biological product be licensed by FDA. 6/ Biologics license applications

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6/ FDA regulates biological products that travel in interstate commerce. FDA has determined that the required nexus with interstate commerce exists for somatic cell therapy products. In a 1993 policy statement, FDA stated:

> 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 [FD&C] Act. . . . . 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)).

58 Fed. Reg. 53248 (Oct. 14, 1993) ("Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products") (the "Somatic Cell Therapy Policy"). Accordingly, somatic cell products are subject to FDA regulation whether or not they are shipped across state lines.

("BLAs") are issued upon a showing that the establishment and product meets "standards, designed to insure the continued safety, purity, and potency of such products. . . ." *Id.* at § 351(d); 42 U.S.C. § 262(d). Data to support licensure of a biological product usually must be developed through nonclinical and clinical research. While a biological product is under clinical investigation, it must meet FDA's investigational new drug ("IND") requirements set forth in 21 C.F.R. part 312. 21 C.F.R. § 601.2. 7/

FDA's IND regulations require that prior to conducting clinical trials, a company submit an IND application to FDA, setting forth its protocols for the study and the scientific basis for believing the product would be safe and effective for particular use(s) in humans. The study may begin within 30 days following submission of an IND application, unless FDA advises otherwise or requests additional time to review the application. Clinical trials generally are conducted in three phases. Once trials have commenced, FDA may stop the trials by placing a "clinical hold" on them because of concerns about, for example, the safety of the product being tested. In addition, all

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This same logic would apply to all cellular materials that are used in the prevention, treatment, or cure of a disease or condition of human beings.

7/ Biological products are also considered drugs under the FD&C Act and, therefore, are subject to the FD&C Act's investigation, adulteration and misbranding provisions. 21 U.S.C. §§ 351, 352.

clinical studies must be approved and conducted under the supervision of the Institutional Review Board ("IRB") responsible for the study. 8/

The key elements of the PHS Act framework have been virtually unchanged since its enactment in 1944. As set forth in greater detail in Section V, this framework has been able to remain in place because FDA has always retained the flexibility to address novel issues created by new technologies. Keeping up with continuing advances in the field of modern biotechnology, FDA issues guidance documents or policy statements to describe whether and how its current statutory and regulatory authority applies to a new technology. FDA issued such a document regarding somatic cell therapy in 1993. 9/ While this document itself does not provide a complete basis for the regulation of the Cellular Materials involved in human cloning, it illustrates FDA's authority to regulate emerging products under the PHS Act. Moreover, this 1993 document is a first step towards the issuance of FDA's 1997 Proposed Approach to the Regulation of Cellular and Tissue Based Products (described below), which fully describes the basis for regulating the Cellular Materials that would be involved in human cloning.

8/ Clinical investigation of a product is critical prior to its approval. In fact, the widely publicized successful cloning of the sheep "Dolly" was only accomplished after 276 failed attempts. This high failure rate reflects the risks associated with this process and the need for extensive investigation in animals to assure the safety of these Cellular Materials before any use in humans is seriously contemplated.

9/ *See supra*, Section II for a discussion of the manipulation of somatic cells that occurs in the process of human cloning.

1. FDA Can Regulate Some of the Cellular Materials That Would Be Involved in Human Cloning as Somatic Cell Therapy

Tremendous advances in science and biotechnology in the last decade have resulted in the development of somatic cell therapy. Somatic cell therapy is 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 human beings and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries." 58 Fed. Reg. 53248 (Oct. 14, 1993) ("Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products"). 10/ Somatic cell therapy holds great promise for the treatment of many diseases and conditions. Currently, scientists are studying how they can use somatic cell therapy "to manipulate and use human cells to treat viral infections, Parkinson's disease, diabetes, HIV infection (AIDS), and other diseases and conditions." "Reinventing the Regulation of Human Tissue," National Performance Review (February 1997) at 3.

10/ This definition reflects the definition of biological product contained in the PHS Act prior to the enactment of the Modernization Act. That definition referred to products "applicable to the prevention, treatment, or cure of diseases or injuries of man." 42 U.S.C. § 262(a). Notably, the new definition of biological product contained in the Modernization Act was broadened to refer to products "applicable to the prevention, treatment, or cure of a disease or *condition* of human beings." 42 U.S.C. § 262(i). While infertility is not a disease, it is an abnormal condition. Similarly, cloning a human being in the absence of infertility could initiate the condition of pregnancy.

Somatic cell therapy products fall within FDA's definition of a biological product. 58 Fed. Reg. at 53249. Specifically, under the PHS Act somatic cell therapy products are "blood, blood component or derivative . . . analogous product[s] . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHS Act § 351(i), 42 U.S.C. § 262(i). Accordingly, somatic cell therapy products are regulated as biological products, subject to licensure under section 351 of the PHS Act. Any clinical use of somatic cell therapy products would require compliance with FDA's IND requirements under 21 C.F.R. part 312. 11/

The process of somatic cell nuclear transfer to create a human clone clearly would be the manipulation of a human cell to treat a human disease or condition. Some of the Cellular Materials involved in such manipulation have attributes of somatic cell products, which are regulated as biological products under the PHS Act and are subject to the attendant licensure requirements. 12/

11/ As in the case of somatic cell and gene therapy products, the Cellular Materials involved in human cloning will involve many ancillary products used as part of the process. While such products are not intended to be present in the final products of human cloning, they may have an impact on the safety, purity, or potency of the final products. To the extent ancillary products used in nuclear transfer technology are new devices, or are already marketed as medical devices but not labeled for such specific use, they are subject to regulation by the Center for Devices and Radiological Health (CDRH) under the medical device provisions of the FD&C Act, 21 U.S.C. § 201 *et seq.* Appropriate regulatory control will depend on the status and use of the device and may require an investigational device exemption (IDE) or inclusion in an IND; use by the manufacturer of the device of a master file under 21 C.F.R. § 814.3(d); premarket approval (PMA); or premarket notification (510(k)). *See* 58 Fed. Reg. at 53250.

12/ The other Cellular Materials involved in human cloning, the germ cells, would not be regulated pursuant to FDA's Somatic Cell Policy because, by definition, germ cells are not somatic cells. *See supra*, note 3. Instead, the germ cells involved in human cloning and the somatic cells could both be regulated

> 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. . . . 13/

Because the Cellular Materials involved in human cloning include somatic cells and their derived products, they are biological products. Accordingly, it is within FDA's authority to regulate them under the PHS Act, and to require that they be proven safe and effective pursuant to an IND before being licensed by FDA. 14/

2. FDA Can Regulate the Cellular Materials Used in Human Cloning as a Cellular or Tissue-Based Products

It is within FDA's discretion to regulate the Cellular Materials involved in human cloning as a cellular or tissue-based product. As described above, the rapidly evolving nature of this field necessitates that FDA's policies in this area also be evolutionary. In February 1997, FDA proposed, consistent with its existing statutory framework, a new approach to the regulation of human cellular and tissue-based products. This framework is intended to "protect the public health without imposing

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as cellular-based products under FDA's Proposed Approach to Cellular and Tissue-Based Products, described *infra*, at Section III.A.2.

13/ 58 Fed. Reg. at 53250.

14/ The Cellular Materials also have attributes of gene therapy products, which are also regulated as biological products by FDA. "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 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." 58 Fed. Reg. at 53249-50.

unnecessary government oversight." "Reinventing the Regulation of Human Tissue," National Performance Review (February 1997) at 1.

The 1997 document establishes the further evolution of FDA's application of the PHS Act to cellular products. While still a proposed approach, it correctly recognizes that the existing statutory authority in the PHS Act can be applied not only to somatic cells but also to a broader array of materials, including germ cells.

The framework proposes a tiered approach to the regulation of cellular and tissue-based products. FDA, "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" (February 28, 1997) (the "Proposed Approach"). Products that pose increased risks to health or safety would be subject to increased levels of regulation. For example, products that pose little risk of transmitting infectious disease would be subject to minimal regulation (*i.e.*, facility registration and product listing). However, products that are (1) highly processed (more-than-minimally manipulated), (2) are used for other than their normal purpose, (3) are combined with non-tissue components (*i.e.*, devices) or (4) are used for metabolic purposes (*i.e.*, systemic, therapeutic purposes) will be required to be clinically investigated under INDs and subject to BLAs. Moreover, they would be licensed only if FDA determines they are safe, pure and potent under section 351 of the PHS Act. *Id.* at Table 1.

Recalling that the Cellular Materials involved in human cloning would include both somatic (non-reproductive) cells and enucleated oocytes (germ line or

reproductive cells without a nucleus), it is important to note that the Proposed Approach is applicable to both germ line and somatic cells. In this way it differs from previous FDA documents, such as the 1993 Somatic Cell Therapy Policy, which did not address the application of the PHS Act to germ line cells.

Although FDA has not yet implemented all aspects of the Proposed Approach, the statutory authority to do so already exists. Moreover, within the proposed framework as currently envisioned, it appears that FDA could regulate the Cellular Materials involved in human cloning as biological products. 15/

a. Non-homologous function. For example, the Cellular Materials involved in human cloning may be regulated as biological products because they are used for a non-homologous function (*i.e.*, the nucleus of a somatic (or non-reproductive) cell is transferred to a reproductive cell). By focusing on the use of the donor (somatic) cell, it is readily apparent that the intended reproductive use of somatic cells is different from their "native function." 16/ This dramatic alteration of the natural functions of the Cellular Materials involved in human cloning poses significant safety and efficacy concerns. FDA has "increased safety and effectiveness concerns for cellular and tissue-based products that are used for non-homologous function, because

15/ While FDA may choose to implement this policy through regulation, FDA also may implement it on a case-by-case basis. *See infra*, Section IV.

16/ FDA, *Proposed Approach* at 15, 26.

there is less basis on which to predict the product's behavior." Proposed Approach at 16.

b. More-than-minimal manipulation. At least some of the Cellular Materials involved in human cloning may be regulated as biological products because they are more-than-minimally manipulated or are used in the production of products used in cloning whereby the materials may themselves be classified as biologics or medical devices in accordance with FDA's Somatic Cell Therapy Policy. In some cases, such as enucleated oocytes, the cells are highly manipulated. Because the fundamental nature and function of the recipient cells would be changed through fusion with reproductive cells, the process would constitute more-than-minimal manipulation. 17/

c. Risk to offspring. FDA also has the discretion to regulate the Cellular Materials involved in human cloning based on the significant health and safety risks inherently associated with these products. While the Proposed Approach does not recommend complex regulation of reproductive tissues, because FDA perceives that "[f]ailure of reproductive tissue generally does not have life-threatening or systemic adverse effects except for fertility per se," the agency clearly did not have

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17/ "More-than-minimal manipulation" is defined as "processing that alters the biological or relevant functional characteristics of cells or tissue." *Id.* at 26. *See also id.* at 14. ("Examples of more-than-minimal manipulation of cells and tissues include cell expansion, encapsulation, activation, or genetic modification.")

cloning in mind. 18/ Shifting the focus, however, from the effects on the "parents" to the intended goal of the process (a live infant), reveals the dual nature of the procedure which does present risks of adverse effects *on the offspring*. (Recall that before "Dolly" was successfully cloned there were 276 failed attempts at cloning and there have been reports of abnormalities in the offspring. 19/) Moreover, the nature, severity, and frequency of the potential adverse effects are currently unknown. While FDA wisely has not applied the licensure requirements of the PHS Act to the traditional process of *in vitro* fertilization, many of the Cellular Materials described herein are dramatically altered from their normal status and, thus, patently raise significantly greater health risks that must be investigated prior to commercialization.

Consistent with the policies underlying the Proposed Approach, FDA may subject these Cellular Materials to the premarketing approval requirements for biologics under the PHS Act. As the FDA prudently notes, "products may be unsafe because they are ineffective . . . or because they *function improperly*." 20/ The improper functioning of cloned cells in a reproductive setting present risks to the products of conception (human beings) that are currently unknown, but may be life-threatening or permanently disabling. Accordingly, FDA could exercise its regulatory authority to

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18/ *Id.* at 16-17.

19/ Wilmut, *et al.*, 385 *Nature* 810.

20/ *Proposed Approach* at 18 (emphasis supplied).

require demonstration that the Cellular Materials involved in human cloning are safe and effective.

B. FDA Has the Statutory Authority to Regulate the Cellular Material Used in Human Cloning Under Section 361 of the PHS Act

Section 361 of the PHS Act authorizes the Department of Health and Human Services ("HHS") to "make and enforce such regulations as in [its] judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." 42 U.S.C. § 264. This provision provides the agency with broad discretion to enact regulations necessary to prevent the spread of communicable diseases.

Section 361 serves as the basis on which FDA currently regulates human tissue intended for transplantation. 21 C.F.R. parts 16 and 1270. *See* 62 Fed. Reg. 40429 (July 29, 1997) ("Human Tissue Intended For Transplantation"). 21/ Section 361 also has served as the basis under which FDA has regulated the source and use of potable water, milk pasteurization, and the transmission of communicable disease through shellfish, turtles, certain birds, and bristle brushes. *Id.* at 40431. *See State of*

21/ The final rule covering human tissue intended for transplantation covers such basic, minimally manipulated tissue as corneal tissue, bones, skin, or tendons. It does not address highly manipulated tissue such as the Cellular Materials involved in cloning.

Louisiana v. Mathews, 427 F. Supp. 174 (E.D. La. 1977) (FDA regulation issued pursuant to section 361 of PHS Act banning the sale and distribution of small turtles was permissible as necessary to prevent spread of communicable disease). Section 361 also serves as the basis on which FDA has imposed requirements to protect the nation's blood supply. *Id.*

As evidenced by this discussion, section 361 of the PHS Act provides FDA with broad authority to enact regulations necessary to protect the public health by preventing the spread of communicable disease. FDA, therefore, clearly could regulate human cloning under section 361 of the PHS Act because the transfer of genetic material itself or other cellular components of the cells could convey communicable diseases such as AIDS, hepatitis, and herpes simplex.

IV. FDA Has the Discretion to Regulate the Cellular Materials That Would Be Used in Human Cloning. Moreover, FDA's Discretion is Entitled to Great Deference.

Although, as described above, the PHS Act sets forth the basic framework for the regulation of biological products, Congress gave FDA significant discretion regarding the manner in which FDA approves and regulates these products. This is entirely appropriate given the rapidly changing nature of biotechnology.

Today there is a vast array of biological products that have been approved by FDA and many others that are awaiting FDA action. 22/ These products are

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22/ Today biological products are available or under development to treat, diagnose, or prevent virtually every serious or life-threatening disease. Available products include, but are not limited to,

scientifically complex and rarely lend themselves to categorization. As a result, FDA invariably is required to determine on a case-by-case basis whether its existing statutory authority applies to a new product and, if so, what constitutes adequate proof of safety, purity, and potency (efficacy). The decision whether and how to regulate a product is made based on FDA's expert determination -- in light of the particular facts and circumstances and based on the applicable statutory and regulatory criteria as well as the state of FDA's scientific understanding at the time of the approval. The statute and regulatory scheme delegate this determination to FDA's discretion and expertise.

That was a wise policy decision by Congress. The success of the approval process for biological products is in many ways dependent upon FDA's discretion to respond as it sees fit to any particular biological product within the basic statutory and regulatory framework discussed above. Otherwise, FDA would be unable to respond to the almost daily developments in biotechnology and the complex scientific issues presented by each particular BLA. Absent this discretion, the biological product approval process would grind to a halt.

When FDA exercises the significant discretion provided to the agency by Congress, FDA's exercise of this discretion is entitled to great deference. *U.S. v.*

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vaccines (manufactured both in traditional ways and through the use of biotechnology); human blood and blood-derived products; monoclonal or polyclonal immunoglobulin products; human cellular (*i.e.*, gene therapy) products; protein, peptide and carbohydrate products; protein products produced in animal body fluids by genetic alteration of the animal (*i.e.*, transgenic animals); animal venoms; and allergenic products.

Rutherford, 442 U.S. 544, 553 (1979); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996). In a recent challenge to FDA's approval of a biological product under the PHS Act, the District Court for the District of Columbia held that "FDA's policies and its interpretation of its own regulations will be paid special deference *because of the breadth of the Congress' delegation of authority to FDA and because of FDA's scientific expertise.*" *Berlex Laboratories, Inc. v. FDA et al.*, 942 F. Supp. 19 (D.D.C. 1996) (emphasis added). *See also Lyng v. Payne*, 476 U.S. 926 (1986).

Moreover, even if FDA has not asserted jurisdiction previously with regard to reproductive tissue, for example, it is appropriate that FDA's policies in this area are evolutionary. The Supreme Court has recognized that agency interpretations are not "carved in stone. On the contrary, the agency . . . must consider varying interpretations and the wisdom of its policy *on a continuing basis*." *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 863-64 (1984) (emphasis added). Furthermore, the Court has acknowledged that "regulatory agencies do not establish rules of conduct to last forever. . . . [A]n agency must be given ample latitude to 'adapt their rules and policies to the demands of changing circumstances.'" *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983) (citations omitted).

The recent case *Coyne Beahm, Inc. v. FDA*, 966 F. Supp. 1374 (M.D.N.C. 1997), is instructive. In *Coyne Beahm*, the court considered a challenge to the FDA's assertion of jurisdiction to regulate tobacco products -- an assertion that represented a complete change in policy from the FDA's former position. In determining whether Congress had withheld from the FDA jurisdiction to regulate tobacco products, FDA argued -- and the court agreed -- that FDA was entitled to amend its former interpretation of the FD&C Act. *Id.* at 1384.

Similarly, if FDA were to determine that, given the current state of science and the risks presented to offspring, it is now appropriate to regulate reproductive tissue such as the Cellular Materials involved in human cloning, it is within FDA's discretion to do so. Moreover, given the discretion accorded to FDA under the PHS Act and the agency's scientific expertise, it is appropriate to allow FDA to determine how to regulate the products involved in human cloning consistent with protection of the public health. *See id.* 1384.

V. Conclusion

There is no legal impediment to FDA asserting jurisdiction over human cloning. Indeed, FDA's existing broad statutory and regulatory authority provides FDA with the discretion to assert jurisdiction. Moreover, such an assertion is consistent with FDA's previous activity in this area. Ultimately, the issue of whether and on what basis

FDA asserts such jurisdiction should be based solely on FDA's decision as to what best both protects and promotes the public health.

Robert P. Brady
Molly S. Newberry

Human Clone Research Will Be Regulated; FDA Asserts It Has Statutory

January 20, 1998 - Daily Ink

Authority To Regulate Attempts at Human Cloning

The Washington Post via Dow Jones

Publication Date: Tuesday January 20, 1998

A Section; Page A01

By Rick Weiss

Washington Post Staff Writer

The Food and Drug Administration has decided it has the authority to regulate human cloning, and agency officials warned yesterday that it would be a violation of federal law to try the procedure without its approval.

"Through the Food, Drug and Cosmetic Act we do have the authority to regulate human cloning, and we are prepared to assert that authority," acting FDA Commissioner Michael A. Friedman said in an interview.

The unambiguous declaration by FDA officials confirmed what the agency and Health and Human Services Secretary Donna E. Shalala have hinted at since a Chicago-area scientist announced last month that he would try to clone a person: Human cloning is a form of cellular or genetic therapy that requires prior approval by FDA reviewers.

That means anyone who wants to attempt human cloning legally must file a formal application with the FDA, which would then undertake a lengthy review, Friedman said. The FDA will initiate legal action against anyone who fails to file that application, he said.

President Clinton banned the use of federal funds for human cloning research last March, after scientists in Scotland announced they had cloned an adult sheep. But legislation to ban privately funded human cloning research stalled in Congress last session. And public fears that someone might try the feat flared anew when Illinois scientist G. Richard Seed announced he would try to clone a person before Congress enacted a ban.

After reviewing the issue for several weeks, Friedman yesterday said the FDA had determined that the kinds of manipulations involved in human cloning presented "serious health and safety issues" for the fetus and the mother.

Another FDA official, speaking on the condition of anonymity, said would-be cloners would have to go through a formal procedure that includes the filing of an "investigational new drug application" (IND), which is what drug companies must submit when they want to test new medicines on people.

The IND process requires researchers to prove to the satisfaction of the FDA that their proposed experiment does not pose unreasonable risk of harm to human subjects -- a task that currently would be difficult for human cloning, given the overwhelming failure rate in animal cloning experiments. "They will have to answer questions like, `Have you established animal models? Can you improve the odds? Have you looked at safer alternatives?' " the official said.

Moreover, the official said, given the controversy surrounding the issue of human cloning, the agency might require public hearings as it did last year while it was considering how to regulate the transplantation of animal organs into people.

"It should be done in the open," the official said. "Going through the FDA regulatory pathways, everyone has a say and we face our fears in public and discuss them."

Seed said last night he would have to think about whether to challenge the FDA's legal interpretation, or simply move his cloning effort offshore, as he has said he would do if Congress tried to interfere with his plans. "I'm going to have to talk with a lawyer," he said. "I'd have to evaluate on what basis they're saying this -- what clause of which law."

The FDA officials' comments came amid mounting pressure from scientific organizations that the agency make a clear statement about its regulatory authority over cloning, and as an increasing number of congressional representatives announced they would introduce legislation to ban human cloning.

Scientific groups have become concerned that some of the bills aimed at preventing human cloning would inadvertently or intentionally preclude other kinds of research. A plain statement about the FDA's authority over cloning might take some pressure off Congress, sources inside and outside the administration said, and allow legislators time to craft more carefully worded legislation.

A bill proposed by President Clinton and supported by various scientific organizations has failed to gain any sponsors.

The one bill that has already been approved by the House Science Committee, sponsored by Rep. Vernon Ehlers (R-Mich.), would ban not only human cloning but also human embryo research -- a controversial arena of research that for years has been mired in the debate over abortion.

Federal funding for human embryo research has been banned in this country on an annual basis since 1994 through appropriations language imposed by Congress. But the Ehlers bill would codify that ban as law and make it much more difficult to reverse -- a situation that concerns scientists who believe that studies of human embryos could lead to breakthroughs in fertility, genetics and cancer.

"We think the issue of cloning a human being is a critical and distinct issue, and it's wrong to steer it into the political maelstrom of the abortion debate," said Carl Feldbaum, president of the Washington-based Biotechnology Industry Organization, which represents about 750 biotechnology and academic research institutes and supports a carefully worded ban on human cloning. "The abortion debate, frankly, will not be settled in 1998 or '99," Feldbaum said, "while the issue of cloning human beings deserves to be resolved, and can be."

Last week, Feldbaum sent an open letter to Shalala encouraging her to assert HHS's authority over cloning in the hope that Congress would not rush into a broad research ban. In yesterday's edition of BioCentury, a San Carlos, Calif.-based biotechnology industry newsletter, Philip D. Noguchi, director of the FDA's division of cellular and gene therapies, said for the first time that the agency had firmly decided that human cloning involves "more than minimal manipulation" of human cells. That standard,known in FDA parlance as MTMM, has great meaning within the agency: It is the dividing line between human tissue experiments that do and do not require prior approval from the FDA.

Meanwhile, last week, Rep. Cliff Stearns (R-Fla.) joined the growing list of congressmen who have announced they would submit legislation to ban human cloning. That could delay action on the Ehlers bill, since Stearns heads the Commerce Committee that was the Ehlers bill's next stop. Sen. Dianne Feinstein (D-Calif.) said Friday she too would submit human cloning legislation, the first Democrat to do so.

(END)

Politics & Policy: Human Cloning

Washington: FDA claims oversight

By Steve Usdin
Contributing Editor

WASHINGTON — In a move that might decrease pressure for congressional action, the FDA plans to publicly assert its power to regulate the cloning of humans.

Philip Noguchi, director of the FDA's division of cellular and gene therapies, last week said that FDA has the authority, under regulations on cellular and tissue-based products promulgated last February, to require advance approval for therapies that involve more than minimal manipulation of cells or tissues.

He told BioCentury the agency intends to create a "bright line" demarcating the types of procedures and therapies that can be conducted without prior FDA approval and those that require significant government oversight.

Noguchi said attempts to create a human child through the cloning of cells from a single adult would be subject to FDA regulation.

Noguchi cited another emerging area of fertility treatment over which FDA also will assert its authority. He noted that researchers at New York University and other institutions are experimenting with the use of nuclear transfer technology to transfer the nucleus from human eggs with damaged cytoplasm into healthy eggs that have had the nucleus removed. Although this technique is not cloning — the genetic material comes from both parents — "it is more than minimal manipulation," and as such is subject to FDA oversight, Noguchi said.

In contrast, he said, conventional in vitro fertilization techniques will not be scrutinized.

Noguchi's comments amplified remarks about human cloning earlier this month by HHS Secretary Donna Shalala. "FDA believes it has authority to regulate what would be called an emerging technology," she said. "It would regulate this technology, as it does others, with a view towards protecting the safety of patients and the public health, which means that the FDA has a rigorous process between now and when Congress debates the legislation that could be used in this particular case. No one could go forward without submitting a request to the FDA."

Shalala added that she could not predict FDA's response to an application to clone a human.

FDA action is not likely to prevent Congress and many state legislatures from passing anti-cloning legislation, but it might slow them down enough to ensure that the bills do not inadvertently restrict non-controversial biomedical research.

Biotechnology Industry Organization President Carl Feldbaum wrote to Shalala last week recommending that senior officials within HHS make a public statement noting that FDA has authority to regulate nuclear transfer technology.

The letter noted that several members of Congress "have recently expressed interest in legislation that would ban the cloning of human beings. They may not be aware that the Food and Drug Administration has broad authority to regulate biological products."

Feldbaum also said that for the foreseeable future, FDA should issue a clinical hold on any IND submission to proceed with human cloning experiments.

BIO, FDA, and the Clinton administration have been trying to keep cloning issues separate from controversies over abortion and research on human embryos. House Majority Leader Rep. Richard Armey (R-Texas) has called for urgent enactment of sweeping anti-cloning legislation to stop "mad scientists." Both Armey and Rep. Vernon Ehlers (R-Mich.), who introduced legislation to ban human cloning last year, intend to include a wide ban on research involving human embryos.

Both BIO and PhRMA have repeatedly stated that they support a ban on human cloning, but Feldbaum and PhRMA President Alan Holmer have said that Ehler's legislation as well as President Clinton's proposed bill would inhibit biomedical research.

Neither association has offered a definition of human cloning that would otherwise protect research and therapies. However, the Federation of American Societies for Experimental Biology (FASEB) has drafted one. FASEB's Public Affairs Executive Committee has endorsed a resolution calling for a five-year "moratorium on cloning human beings, where 'cloning human beings' is defined as the duplication of an existing or previously existing human being by transferring the nucleus of a differentiated, somatic cell into an enucleated human oocyte, and implanting the resulting product for intrauterine gestation and subsequent birth."

Europe: Anti-cloning declarations get louder

By Mike Ward
Editor, Europe

OXFORD — European industrialists are on fire watch as Europe's politicians toy with draconian controls on cloning technologies. Members of the European Parliament (MEPs) late last week demanded an outright ban on all human cloning research, taking a much harder line than the protocol signed by 19 members of the Council of Europe.

MEPs not only called on European Union governments to sign and ratify the human cloning protocol, they demanded that each EU member "enact binding legislation prohibiting all research on human cloning within its territory and providing criminal sanctions for any breach".

Prompted by the news that U.S. physicist Richard Seed intended to start cloning humans commercially, the MEPs demonstrated that their opposition to cloning goes much further than most EU countries. Indeed, they noted that "the cloning of human beings, whether carried out on an experimental basis, in the context of fertility treatments, preimplantation diagnosis, for tissue transplantation, or for any other purpose whatsoever, is unethical, morally repugnant, contrary to respect for the person and a grave violation of fundamental human rights which cannot under any circumstance be justified or accepted."

While the MEPs conceded that scientific research is one of the keys to human progress, they stressed that that pursuit must not undermine the dignity and integrity of the human being. Consequently, they asked for confirmation that EU funds will not

See next page

Washington Notebook

PDUFA report card

WASHINGTON — FDA issued its internal report card on review times and numbers of products approved in 1997 *(see Online Links, A4)*. The Center for Drug Evaluation and Research (CDER) announced that the median time to approve new drugs was 14.4 months in 1997, a 6 percent improvement over 1996. The median CDER review time for new drug applications, including those deemed unapprovable, was 12.2 months, an 18 percent improvement over 1996. All CDER applications are reviewed under user fee guidelines.

New molecular entities accounted for 38 of the 121 new drugs reviewed by CDER.

The Center for Biologics Evaluation and Research completed 35 "major" approvals in 1997, including product and biological licenses and 11 supplemental approvals that were part of the user fee program, as well as approvals of software and new manfacturing methods to improve the safety of blood products and biologics.

CBER said its median time for user fee approvals was 14.5 months, 20 percent faster than in 1996. The median time for approval of PLA/BLA supplements for user fee products in 1997 was 10.8 months, down from 12.3 months in 1996.

The median time for first-time approvals at CBER in 1997 was 12 months, a 20 percent reduction from 1996.

PhRMA released its own figures last week indicating that the mean approval time for new drugs in 1997 was 16 months, down from 17.8 months in 1996.

The mean approval time for new drugs in 1992, the last year before FDA began collecting user fees, was 29.9 months.

CDER's Phase IV office

FDA's Center for Drug Evaluation and Research (CDER) is establishing a new office that will track Phase IV trials and monitor adverse event data.

The Office of Post-Marketing Drug Risk Assessment (OPMDR) will be officially established in the first half of the year, said CDER spokesperson Patricia DeSantis. An acting director, Ralph Lillie, already has been appointed to serve until a physician with experience dealing with adverse reactions can be nominated for the permanent position, she said.

The OPMDR is being created in part as a response to provisions in the FDA Modernization Act of 1997, which mandate tracking of Phase IV studies that sponsors agree to conduct as a condition for fast track approval. Product approvals, particularly when they are based on surrogate markers, are often contingent on agreements to submit results from Phase IV trials.

Sen. Edward Kennedy (D-Mass.) and other members of Congress expressed concern last year when they learned that FDA had no mechanism for tracking compliance with commitments to conduct post-marketing trials.

CDER recently established a new Phase IV tracking system *(see Online Links, A4)*.

Concerns raised regarding the collection of adverse event data on Fen-Phen and Redux also were factors in CDER's decision to upgrade existing functions to the status of an independent office.

The Center for Biologics Evaluation and Research has no plans to implement new procedures for tracking Phase IV trials of adverse events, according to a spokesperson for the center.

PhRMA shot at generics

PhRMA President Alan Holmer last week said the pharmaceutical trade association has met with members of the Clinton administration and Congress as part of a campaign to extend the exclusivity of new drugs under the Hatch-Waxman Act to 10 years. Under the act, FDA currently won't review applications for generic competitors for five years.

Europe,
from previous page

finance human cloning research. Moreover, they have called on the United Nations to take all the necessary steps to bring about a legally binding universal and specific ban on human cloning.

Last week, the Brussels-based industry lobby groups EFPIA (European Federation of Pharmaceutical Industry Associations) and EuropaBio both restated their opposition to the cloning of entire human beings.

"The pharmaceutical industry considers that behind every effort to push back the limits of science, man should remain the beneficiary and not the subject of research itself," said EFPIA President Rolf Krebs. However, industry is arguing that it should not be barred from using genetic information that could be used to prevent and cure diseases.

"The pharmaceutical industry is aware that this achievement will not be possible without the application of new technologies, such as the cloning of cells, which is well defined and established as a valuable technique in the search for new ways to treat diseases," added EFPIA.

Both associations said they welcome the Council of Europe's protocol because it places a ban on human cloning while allowing the cloning of cells for research.

The Council of Europe protocol, which is to become a part of the European Convention on Human Rights and Biomedicine, will become binding on the signatories as soon as it has been ratified in five states. The protocol commits the signatories to prohibit "any intervention seeking to create human beings genetically identical to another human being, whether living or dead."

So far the Council of Europe members to have signed up are Denmark, Estonia, Finland, France, Greece, Iceland, Italy, Latvia, Luxembourg, Macedonia, Moldova, Norway, Portugal, Romania, San Marino, Slovenia, Spain, Sweden, and Turkey.

However, Britain and Germany, Europe's leading biotech nations, have balked at putting their signatures to the protocol. Britain is not yet a signatory to the European Convention on Human Rights and Biomedicine, while Germany claims that the measure is weaker than a current law that forbids all research on human embryos — a legacy of the Nazi eugenics program.

Britain's Human Genetics Advisory Commission is putting the final touches to a consultation paper setting out the potential benefits of allowing research into human cloning.

FDA HAS AUTHORITY TO REGULATE CLONING TECHNOLOGY AS BIOLOGIC PRODUCT under the Public Health Service Act, according to an agency representative. Manipulated cells and nucleic acid are considered biologic products, placing the technology of cloning under the jurisdiction of the FDA, the official said.

As an example of other "manipulated cells" regulated by the FDA, the agency official cites FDA's August approval of Genzyme's ***Carticel***, a product that enables damaged cartilage cells, naturally incapable of regeneration, to be repaired. The cell therapy technology developed by the Cambridge, Massachusetts-based biotechnology company involves "harvesting and isolating normal cartilage cells from the knee, culturing and expanding them in the laboratory and then implanting them in the knee," an FDA document explains.

Consideration of FDA's role in the regulation of cloning was sparked by the recent announcement that Richard Seed, an unaffiliated Chicago physicist, plans to establish a fertility clinic to clone human beings.

FDA's authority to regulate cloning would require that sponsors of experiments involving the cloning of human beings go through FDA's investigational new drug (IND) process. Possible FDA sanctions that would be applicable to Seed's proposed experimentation include placing trials on clinical hold and disqualifying investigators. In addition, the agency could seek judicial measures, such as a temporary injunction or a restraining order, against Seed, according to FDA.

In response to Seed's announcement, Sen. Christopher Bond (R-Mo.) announced Jan. 7 that he would sponsor an "emergency ban" on human cloning experimentation when Congress reconvenes in late January. The bill, which is currently being drafted, would ban publicly and privately funded human cloning.

"While we may be prepared from a technological standpoint to proceed with this research, we are not prepared from an ethical standpoint," according to Bond. "There are some avenues which should be off-limits to science," he said. Bond has introduced S 386, a bill to ban federal funding of human cloning. The legislation has been referred to the Senate Labor and Human Resources Committee.

Separately, President Clinton urged in his Jan. 10 radio address that Congress "act now to make it illegal for anyone to clone a human being."

"When it comes to a discovery like cloning, we must move with caution [and]...concern about the impact of our actions," he said. "That's why I sent legislation to Congress last June that would ban the cloning of human beings for at least five years." Congress has not acted on the legislation; Clinton said that "it is now clearer than ever the legislation is exactly what is needed."

In a June 6 report, the National Bioethics Advisory Commission (NBAC) advocates enactment of "carefully and narrowly focused legislation to prohibit, in both the public and private sector, the attempt to create a child using adult nuclear transfer techniques." The commission also supports inclusion of a "sunset clause" in order to revisit the issue after the first five years and every two years thereafter.

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Bio

BIOTECHNOLOGY INDUSTRY ORGANIZATION

January 13, 1998

The Honorable Donna E. Shalala, Ph.D.
Secretary,
Department of Health and Human Services
615F Hubert H. Humphrey Building
200 Independence Ave., SW
Washington, DC 20201

Dear Secretary Shalala:

The recent announcement from Dr. Richard Seed regarding his proposal to establish a clinic for the cloning of human beings has caused significant controversy. BIO supports President Clinton's and the National Bioethics Advisory Commission's (NBAC) moratorium on the cloning of a human being. Cloning a human being poses major ethical and moral questions, as well as deeply troubling medical safety issues. The experience with "Dolly," in which there were 276 unsuccessful attempts before an apparently healthy sheep was born, points to the experimental nature of this technology in animals. It is plainly inappropriate to attempt to apply this technology to human beings. While these questions remain unresolved, government and public opposition to the cloning of a human being remains strong. Society needs to be heard and respected on this issue.

Several members of Congress have recently expressed interest in legislation that would ban the cloning of human beings. They may not be aware that the Food and Drug Administration (FDA) has broad authority to regulate biological products. Last February, FDA published a regulatory framework for the regulation of cellular and tissue-based products. The level of FDA oversight is dictated by the degree of human manipulation of cells or tissues. Those products which are subject to a low level of oversight are those which are defined as 'minimal manipulation' when the processing does not alter the biological characteristics of the cells or tissue.

But in those cases where there is more than 'minimal manipulation,' FDA has stated its intent to subject such products to formal regulatory review including the investigational new drug (IND) regulations and license review regulations.

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Page Two

BIO believes that the Dr. Seed's proposal to clone humans using nuclear transfer technology is much more than minimal manipulation as the original function of the egg cell is unmistakably altered by the removal of the parental haploid DNA and insertion of DNA from a somatic cell from another person. Thus, any such research along these lines should be subject to the IND regulations that require patient informed consent, review by an institutional review board (IRB) where the research is being conducted, and FDA review under 21 CFR Part 312.

In addition to raising profound ethical issues, nuclear transfer technology has not been reliably proven to work in animal models and raises serious safety issues. We believe that for the foreseeable future, FDA should issue a clinical hold on any IND submission to proceed with such experiments.

A public statement by senior officials within HHS as to the regulatory status of nuclear transfer technology would be welcomed and useful as the public debate continues.

Sincerely,

Carl B. Feldbaum
President

CBF:ag

cc: Michael Friedman, MD, Food and Drug Administration