"The Laws Lagging Behind Cloning / Research is Full Speed Ahead, But Bills to Curb it Languish"

By Caroline Daniel. Washington Post

Newsday (New York, NY), August 4, 1998 Health+Discovery, P. C03 FOCUS

measure without a single committee hearing. But patient groups and scientists waged a successful last-minute lobbying campaign, claiming the bill would obstruct important medical research, and the bill, mustering only 42 votes, 18 short of the 60 required, went down in defeat.

Meanwhile, Democrats offered a rival bill sponsored by Sens. Dianne Feinstein (D-Calif.) and Edward M. Kennedy (D-Mass.). This sought to ban the cloning of people, but not human embryos for research purposes. The bill was referred to the Senate Labor and Human Resources Committee, where it sits in quiet obscurity.

The only other cloning bill that made any progress was one introduced by Rep. Vernon Ehlers (R-Mich.), which would prohibit the use of federal funds for human embryo cloning. It was approved by the House Science Committee in July, 1997, and moved to the Commerce Committee, which has yet to place the bill on its agenda.

The sponsors of the various bills this week largely conceded that it will be tough to address the issue before this fall's elections. "The sense I have is that probably nothing is going to happen on this," said Jim Stacey, spokesman for the American Medical Association. "There are so few days left, and there are other things to do."

Stepping into that legislative void, the FDA announced in February that anyone wanting to clone a person would have to apply for permission from that agency. But critics have questioned the legal basis of that claim.

(1)

One concern is whether cloned cells are "medical products," which would place them under the agency's purview, or whether cloning is simply a new variant of fertility treatment. "The FDA is not supposed to regulate the practice of medicine," said Richard Merrill, a professor at the University of Virginia School of Law.

(2)

A second concern is that the FDA has no basis for considering ethical factors - such as the psychological impact of being born a clone - in its decisions.

(3)

A third concern is a technical one, but one that is central to the FDA's case that it has the right to regulate would-be human cloners. It has to do with the amount of cellular manipulation involved in cloning.

The FDA does not always demand prior approval for research on cells that will only be "minimally manipulated." However, if those cells are deemed to be "more than minimally manipulated," the work is subject to FDA regulation.

Cloning involves removing the genetic core, or nucleus, of an egg cell and injecting into that gutted cell the nucleus of another cell from the animal or person to be cloned. "What you're left with is a highly manipulated cell," asserted an FDA official, who spoke on the condition of anonymity.

Some question, however, how the FDA came to that conclusion. They note that in vitro fertilization, or IVF, also involves manipulation of cells, and other fertility techniques are even more aggressive than IVF, but the FDA has not tried to regulate them.

Cloning "may give us the creeps," Freeman said. "But is it 'more than minimal manipulation'? I frankly have a lot of trouble seeing it."

Lori Andrews, a professor of law and bioethics at the Chicago-Kent College of Law, agrees. "The question here is, Why haven't they been regulating analogous procedures such as ICSI an invasive variant of IVF in which sperm are injected directly into eggs , which also has a high-risk profile?"

Both experts also make the point that some forms of cloning - for example if a woman wanted to clone herself - may be safer than traditional IVF, because it involves little risk of passing on a communicable disease, such as AIDS. Under new FDA guidelines, the transfer of cells or tissues back into the individual from whom the cells came requires less oversight by the FDA.

As it turns out, the FDA is not comfortable with its position and has set up a working group to look into such questions. "One could look at it and say ICSI is nothing more than bringing two gametes together and allowing them to fertilize naturally," the FDA spokesman said. "Or you could say that inserting a needle into an egg and injecting a sperm is altering it. It is a pretty close call."

The FDA working group may have to work fast if it wants to settle such issues before the first human clone arrives. Scientists said last week that the first human clones could be born in the next five years or so. And Seed, in a telephone conversation last week, said he was "vigorously" pursuing his goal.

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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

URGENT

Monday, February 9, 1998

LEGISLATIVE REFERRAL MEMORANDUM

TO:	Legislative Liaison Officer - See Distribution below
FROM:	Janet R. Forsgren (for) Assistant Director for Legislative Reference
OMB CONTACT:	Robert J. Pellicci
	PHONE: (202)395-4871 FAX: (202)395-6148
SUBJECT:	**HHS Report on S1601 Human Cloning Prohibition Act**
DEADLINE:	**NOON Monday, February 9, 1998**

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President. **Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.**

* **COMMENTS:** Senator Kennedy has requested the attached letter for use during tomorrow's debate on S. 1601. **DEADLINE IS FIRM.** *

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LRM ID: RJP190 **SUBJECT:** HHS Report on S1601 Human Cloning Prohibition Act

RESPONSE TO
LEGISLATIVE REFERRAL
MEMORANDUM

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet. If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.

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TO: Robert J. Pollicci **Phone:** 395-4871 **Fax:** 395-6148
Office of Management and Budget
Branch-Wide Line (to reach legislative assistant): 395-7362

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_____ Concur

_____ No Objection

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DRAFT

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Labor and Human Resources
United States Senate
Washington, D.C. 20510-6300

Dear Senator Kennedy:

This is in response to your inquiry concerning the jurisdiction of the Food and Drug Administration (FDA) over human cloning activities. Apparently, some are suggesting that immediate Federal legislation is necessary to prevent the commencement of human cloning experiments that are intended to result in the creation of a human being through cloning techniques. FDA has jurisdiction over such experiments and is prepared to exercise that jurisdiction.

Human cloning is subject to FDA regulation under the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. Under these statutes and implementing FDA regulations, clinical research on human cloning may proceed only when an investigational new drug application (IND) is in effect. Before such research may begin, the sponsor of the research is required to submit to the FDA an IND describing the proposed research plan, to obtain authorization from an independent institutional review board, and to obtain the informed consent of all participating individuals. FDA may prohibit a sponsor from conducting the study (often referred to as placing the study on "clinical hold") for a variety of reasons, including

DRAFT

if the agency finds that "[human subjects are or would be exposed to an unreasonable and significant risk of illness or injury," "the IND does not contain sufficient information required ... to assess the risks to subjects of the proposed studies," or "the clinical investigators ... are not qualified by reason of their scientific training and experience to conduct the investigation." At a minimum, the sponsor must wait at least 30 days after submitting its proposal to the FDA before beginning any study.

In the case of human cloning experiments, there are major unresolved safety questions. Until those questions are resolved, the agency could not permit any investigation of human cloning to proceed.

I hope this information is useful to you in your deliberations.

Sincerely,

Michael A. Friedman
Lead Deputy Commissioner
Food and Drug Administration

Total Pages: 11

LRM ID: RJP199

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

URGENT

Friday, February 20, 1998

LEGISLATIVE REFERRAL MEMORANDUM

TO: Legislative Liaison Officer - See Distribution below

FROM: Janet R. Forsgren (for) Assistant Director for Legislative Reference
OMB CONTACT: Robert J. Pellicci
PHONE: (202)395-4871 FAX: (202)395-6148

SUBJECT: **HHS Report on FDA's jurisdiction over human cloning activities**

DEADLINE: **NOON Monday, February 23, 1998**

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President. **Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.**

COMMENTS: The attached document would be provided to congressional staff upon request. **CLOSE HOLD OF DOCUMENT IS NECESSARY.**

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LRM ID: RJP199 **SUBJECT:** HHS Report on FDA's jurisdiction over human cloning activities

RESPONSE TO
LEGISLATIVE REFERRAL
MEMORANDUM

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet. If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the General Counsel

Office of the Chief Counsel
Food and Drug Administration
5600 Fishers Lane, GCF-1
Rockville, MD 20857

DRAFT

FDA's Jurisdiction Over Human Cloning Activities

This statement addresses FDA's jurisdiction over human cloning activities. FDA's jurisdiction over products used in cloning activities derives from the biological products provisions of the Public Health Service Act (PHS Act) and the drug provisions of the Federal Food, Drug and Cosmetic Act (FD&C Act).[1]

I. Background

The term clone means a precise copy of a molecule, cell, or individual plant or animal. National Bioethics Advisory Commission, *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission* (NBAC Report) app. 1 (June 1997). In the past year, the issue of cloning has received much media attention. In March of 1997, Scottish researchers announced that they had cloned an adult sheep. The researchers removed an egg from a female sheep and replaced the nucleus of the egg with the nucleus from a somatic cell[2] from another adult sheep. They used electrical pulses to introduce the new nucleus into the egg and to cause the cells to divide. The researchers then implanted the manipulated egg into the uterus of a female sheep, resulting in the birth of a cloned sheep. The technique that resulted in the cloned sheep is referred to as somatic cell nuclear transfer.

Following the announcement of the cloned sheep, President Clinton directed that federal funds should not be used for cloning a

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[1]The medical device provisions of the FD&C Act also apply to some products used in human cloning activities but are not discussed in this statement.

[2]A somatic cell is a cell of an embryo, fetus, child, or adult not destined to become a sperm or egg cell. NBAC Report app.3.

human being. Because the prohibition on the use of federal funds for human cloning did not extend to non-federally funded research, President Clinton asked for a voluntary moratorium on human cloning by privately funded researchers. He also asked the National Bioethics Advisory Commission (NBAC) to address the legal and ethical issues raised by cloning and to submit a report to him. In its June 1997 report, the NBAC concluded that "at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or a clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning." NBAC Report at iii.

For purposes of this statement, the agency assumes that the technique used to clone a human being would be somatic cell nuclear transfer. The cloning process to create a human being would be similar to that used to create the cloned sheep discussed above in that the process would involve the transfer of a cell nucleus from a somatic cell of a human being into an egg from which the nucleus has been removed. The resulting cell (somatic cell clone) produced for the purpose of creating a cloned human being is a product subject to regulation by FDA.

II. Legal Authority

FDA has the authority to regulate numerous medical products, including biological products and drugs. As discussed more fully below, the cellular product and the components of the cellular product used in cloning fall within the definitions of biological products in the PHS Act and drug in the FD&C Act.[3] A product may be both a biological product and a drug. See Celise v. United States, 217 F. Supp. 705, 709 (S.D.N.Y. 1962). The conclusion that FDA has jurisdiction over somatic cell clones under the PHS Act and the FD&C Act is consistent with the statutory purpose of public health protection. Courts have recognized that remedial statutes, such as the FD&C Act

[3]Depending on the specific facts of any cloning process, there may be additional reasons why particular somatic cell clones would be biological and drug products.

and the PHS Act, are to be liberally construed consistent with their public health purpose. See United States v. An Article of Drug ... Bacto-Unidisk, 394 U.S. 784 (1968); United States v. Loran, No. CV 98-4283 SVW (C.D. Ca. Oct. 17, 1997).

A. A Somatic Cell Clone is a Biological Product

FDA regulates biological products under section 351 of the PHS Act. 42 U.S.C. § 262. That section applies to "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment or cure of diseases or injuries of man..." Id. Section 123(d) of the Food and Drug Administration Modernization Act of 1997 (FDA Modernization Act) amends the PHS Act by including within the definition of biological products "conditions" as well as diseases. 42 U.S.C. § 262(i) (effective February 19, 1998).

1. A Somatic Cell Clone is Applicable to a Disease or Condition of Human Beings

As set forth in the PHS Act, a biological product is subject to regulation if it is "applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i) (effective Feb. 19, 1998). A somatic cell clone used to create a cloned human being for an infertile individual is a product applicable to the treatment of infertility. Likewise, a somatic cell clone used to create a cloned human being to avoid transmission of a genetic disease from a prospective parent is a product applicable to the prevention of that genetic disease in the cloned human being. In addition, significant safety questions have been raised regarding whether the cloning process will produce a healthy human being who will develop normally. For example, the cloned human being might have defects from the donor or during development, such as genetic, biochemical, or cellular defects.

2. A Somatic Cell Clone Is An Analogous Product Under the PHS Act

A somatic cell clone is not one of the specifically listed products in section 351 of the PHS Act. It is, however, an "analogous product" under the PHS Act and thus falls within the scope of this section.

The term "analogous" is defined as "resembling or similar in some respects, as in function or appearance, but not in origin or development." Dorland's Medical Dictionary 78(25th ed. 1974). A somatic cell clone has similarities in composition and function with blood and blood components. A somatic cell clone is analogous to white blood cells, a component of blood, in that both cells are similarly composed because they are somatic cells that contain a nucleus. A somatic cell clone is also like blood and blood components in that they contain cellular elements derived from a living human being and are applicable to diseases or conditions of human beings.

A somatic cell clone also is analogous to a toxin or antitoxin as those terms are described in FDA regulations.[4] The recent decision in United States v. Loran, No. CV 98-4283 SVW (C.D. Ca. Oct. 17, 1997) supports such a determination. In Loran, the court addressed whether a cell product consisting of neonatal rabbit and human fetal cells intended for the treatment of diabetes was an analogous product under the PHS Act. The court noted that the government reasonably construed the PHS Act and concluded that the cell product was a biological product. Given the common features between a somatic cell clone and the neonatal rabbit and human cells in Loran, that decision supports a determination that a somatic cell clone is an analogous product. Loran at 4-5, 11.

B. A Somatic Cell Clone Is a Drug

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[4] A product is analogous to a toxin or antitoxin "if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process." 21 C.F.R. § 600.3(h)(5)(iii).

Under the FD&C Act, the term "drug" is defined as "articles (other than food) intended to affect the structure or any function of the body." 21 U.S.C. § 321(g)(1)(C). The term "drug" also includes components of a drug. 21 U.S.C. § 321(g)(1)(D). As described above, a somatic cell clone is a product intended to affect the structure or function (including the diseases or conditions) of the cloned human being. The continued growth and development of the cloned human being are the result of the maturation of the somatic cell clone. In addition, a somatic cell clone could be viewed as a product intended to affect the structure or function of the woman into whose uterus the somatic cell is to be implanted.

A product also is a "drug" if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." 21 U.S.C. § 321(g)(1)(B). A somatic cell clone used to create a cloned human being in order to avoid transmission of a genetic disease from a prospective parent with the disease would be an article intended to prevent the transmission of disease to the cloned human being and thus would fall within this definition. A somatic cell clone used with the intent to create a cloned human being for an infertile couple also could fall within this drug definition in that the product would be used to treat infertility.

A somatic cell clone also is a "new drug" under the FD&C Act in that it is a drug that is not generally recognized by experts as safe and effective to clone human beings. 21 U.S.C. § 321(p). Before new drugs may be marketed, FDA review and approval are required. 21 U.S.C. § 355(a).

III. Previous FDA Guidance on Cellular Products

FDA has issued a number of documents in the past several years addressing products that have similar characteristics to a somatic cell clone product. The agency's notices on somatic cell and gene therapy products and cellular and tissue-based products are consistent with a

determination that a somatic cell clone would fall within FDA's jurisdiction.

A. Regulatory Approach to Somatic Cell and Gene Therapy Products

Although somatic cell products are not specifically listed in the statutory definition of biological product, FDA previously has stated that these products are biological products subject to regulation under the PHS Act and drugs within the meaning of the FD&C Act. In its October 1993 notice, FDA defined somatic cell therapy products as "autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries." 58 Fed. Reg. 53248, 53249 (Oct. 14, 1993). The agency advised persons interested in performing clinical investigations involving these products that FDA's regulations on investigational drugs and biological products apply, and that the products also are subject to the drug requirements of the FD&C Act.

B. FDA's Proposed Regulatory Approach for Cellular and Tissue-Based Products

In March of 1997, FDA announced its proposed regulatory approach for cellular and tissue-based products. See 62 Fed. Reg. 9721 (March 4, 1997). A finding that a somatic cell clone is a biological product and a drug is consistent with the position taken by FDA in its approach to cellular and tissue-based products. The regulatory approach addresses a wide range of products such as skin, bone, and corneas, as well as somatic cell therapy products and gene therapy products. Because a somatic cell clone is a cellular-based product, the regulatory approach would apply.

Under this regulatory approach, FDA announced that it was planning to take a tiered approach to the regulation of cellular and tissue-based products, imposing requirements to the extent necessary to protect the public health. For some products, FDA would impose only requirements related to the prevention of communicable diseases.[5] For products raising additional public health concerns, such as products that undergo more than minimal manipulation or that have a systemic effect on the body, premarket review and approval would be needed.

In the regulatory approach, FDA addressed reproductive tissues and noted that such tissues have a long history of use in the medical community. FDA also recognized that such tissues raise a number of less substantial issues than those raised by other tissues that have a systemic effect on the body. As a result, FDA stated that such tissues would be subject to less regulation than other tissues that have a systemic effect on the body. Unlike the reproductive tissues discussed in the regulatory approach, tissues and cells for cloning of human beings raise additional significant health concerns not raised by processes in place for the reproductive tissues used in the past. Consistent with the tiered approach for cellular and tissue-based products, a somatic cell clone would be subject to FDA premarket review and approval because it is more than minimally manipulated.

IV. Prohibited and Permissible Acts

The FD&C Act prohibits the introduction into interstate commerce of unapproved new drugs and misbranded and adulterated drugs and the holding for sale of such misbranded and adulterated products after shipment in interstate commerce. 21 U.S.C. § 331 (a),(d),(k). The approval of a new drug application removes the prohibition on interstate shipment. The PHS Act also prohibits interstate shipment: "[n]o person shall sell, barter, or exchange, or offer for sale, barter or exchange" in

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[5]For these products, FDA would only regulate the product under the communicable disease provisions of the PHS Act and not under the FDCA or the biological products provisions of the PHS Act. See 42 U.S.C. § 264.

interstate commerce any unapproved biological product. 42 U.S.C. § 262(a). Section 123(a) of the FDA Modernization Act amends the PHS Act by replacing the terms "sell, barter or exchange" with "introduce or deliver for introduction into interstate commerce." 42 U.S.C. § 262(a).

Under the authorities of both Acts, FDA promulgated regulations to allow clinical research on investigational drugs and biological products. Clinical research on these products can proceed only when an investigational new drug application (IND) is in effect. See 21 U.S.C. § 355(i) (authorizing FDA to promulgate regulations for research involving investigational new drugs), 42 U.S.C. § 262, 21 C.F.R. Part 312. Before such research may begin, the sponsor of the research is required to submit to FDA an IND describing the proposed research plan. The sponsor also is required to obtain authorization to proceed from an institutional review board (an independent group of experts and consumers which reviews the proposed study from a scientific and ethical perspective). 21 C.F.R. §§ 56.103, 312.23(a)(1)(iii) and (iv). In addition, the researcher is required to obtain the informed consent of the individuals who are considering whether to participate in a clinical study. See 21 U.S.C. § 505(i), 21 C.F.R. Parts 50 and 312. Thus, before an egg is removed from a woman or the cell containing the nucleus to be inserted into the egg is removed from the prospective genetic parent for the purpose of creating a cloned human being, an IND should be in place and informed consent obtained.

Once FDA receives a proposed study, it reviews the IND application to assess whether it is appropriate for the study to proceed. Among the information reviewed by FDA is information related to the safety of the product, including pharmacology and toxicology information that the applicant believes shows that it is reasonably safe to conduct a clinical investigation. FDA may prohibit a sponsor from conducting the study (often referred to as placing the study on "clinical hold") for a variety of reasons, including if the agency finds that "[h]uman subjects are or would be exposed to an unreasonable and significant risk of illness or injury," "[t]he IND does not contain sufficient information required to assess the risks to subjects of the

proposed studies," or "[t]he clinical investigators ... are not qualified by reason of their scientific training and experience to conduct the investigation..." For example, information raising concerns about the sterility of the product or data from animal studies showing serious adverse reactions in animals would cause FDA to question whether a study should proceed.

V. Regulatory Actions for Violations of the FD&C Act and PHS Act

Where violations of the Acts occur, such as shipment of an unapproved drug or biologic or misbranding or adulteration of a drug, the government has the authority to initiate regulatory actions, including administrative actions (e.g., clinical investigator disqualification proceedings) and civil and criminal litigation (e.g., seizures, injunctions, and criminal prosecution).