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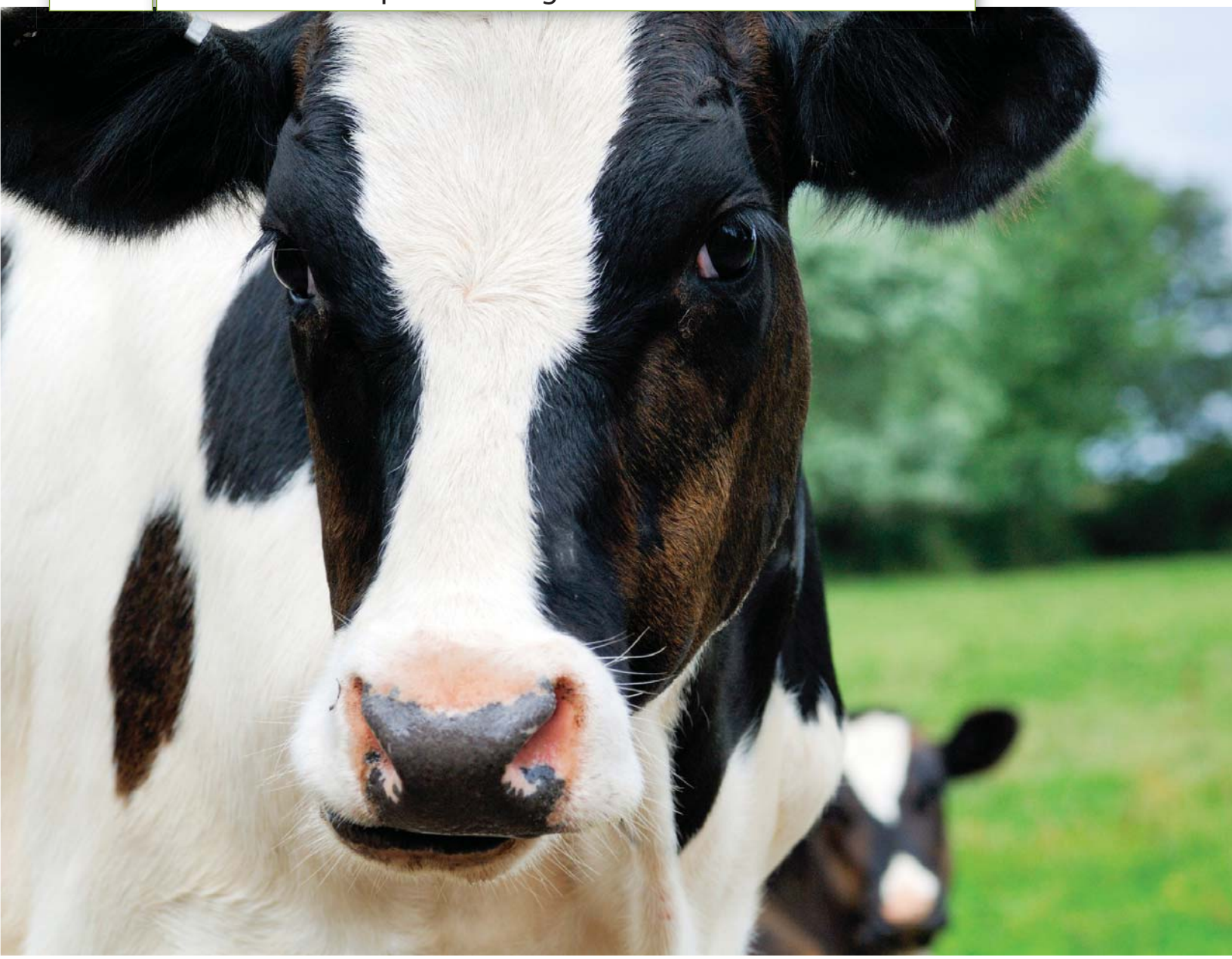
Critical Issue Report: Cloning for Food



Is the FDA's Cloning Proposal Ready for Prime Time?

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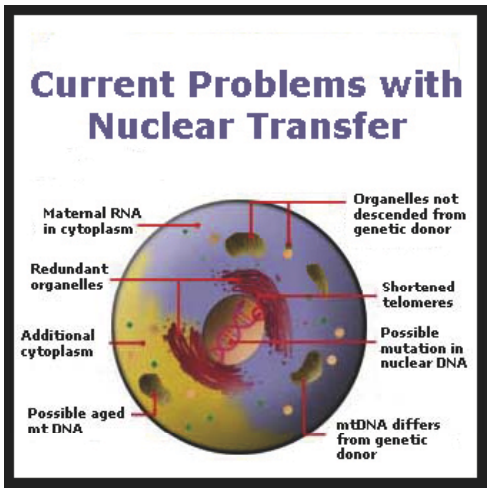
I. Executive Summary

On December 28, 2006, the Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration (FDA) issued a draft risk assessment, a risk management plan, and guidance to industry on meat and milk from cloned animals. A Federal Register notice was issued on January 3, 2007, in which the FDA requested comments on all three documents.

The documents address the risks associated with somatic cell nuclear transfer (SCNT), the most common method used to create cloned animals, and do not address other cloning technologies or risks associated with genetically engineered animals. The document acknowledges that there are ethical, cultural, and religious issues raised by animal cloning. The agency offers to participate in discussions of these issues "…in other fora," but makes clear such considerations are not germane to its conclusions regarding the safety and animal health impacts of animal cloning.

Throughout the FDA risk assessments, the health risks to surrogate mothers used in the cloning process are compared to the risks associated with other "Assisted Reproductive Technologies" (ARTs), such as artificial insemination, embryo transfers and splitting, and in vitro fertilization.



The Organic Center has issued this Critical Issue Report to provide background on the FDA's proposal and the cloning process so that readers can better understand:

- What the FDA found in its scientific assessment and is proposing;
- The impacts of cloning on animal health and reproduction;
- Potential impacts of animal cloning on food quality and safety; and
- The status of cloned animals, their progeny and products in organic agriculture.

The FDA Assessment and Proposal

According to the notice, the FDA developed the draft risk assessment to evaluate the health risks to animals involved in the process of cloning and to identify the food consumption risks, if any, that may result from consumption of edible products derived from animal clones or their progeny.

In a nutshell, the FDA identified no new or worsened food safety risks associated with the consumption of cloned animals, or milk from cloned dairy cows. The FDA expressed this finding in the risk assessment's executive summary by saying the risks from juvenile or adult cattle, pig, and goat clones "pose no additional food consumption risk(s) relative to corresponding products from contemporary conventional comparators."

In two cases the FDA was unable to support a finding of no new or worsened food safety risks. The FDA concluded there was insufficient information to draw a final conclusion regarding food safety risks associated with consumption of meat from cloned sheep. And in the case of just-born bovine calves, the agency said that consumption of these young animals by humans, or placing them into the livestock feed or pet food supply through rendering, "may pose some very limited food consumption risk." The FDA concluded, however, that rendering these animals will not pose such risks in animal feed or to humans consuming animals fed material derived from the clones.

This finding extends, apparently, even to deformed animals that can, under FDA's risk management plan and guidance to industry, enter the livestock feed or pet food supply through rendering. The FDA's risk management plan states, "No feed risks unique to clones were identified. Therefore, as stated in our accompanying Draft Guidance for Industry, it is our current thinking that clones of any age or species could be used in the production of feed for animals without additional restriction especially for clones."

For all species of animals, the FDA concluded that the meat and edible products from the progeny of clones "pose no additional food consumption risk(s) relative to corresponding products from other animals."

The risk assessment encompasses both food safety risks to humans and animals consuming food or feed derived from clones, as well as health risks to the surrogate mothers involved in the cloning process. The FDA concludes that surrogate mothers used to grow out clones are "at increased risk of adverse health outcomes relative to conventional animals." The agency goes on to say "None of these adverse outcomes, however, are unique to cloning." The full meaning of this sentence is not made clear, but implies that the FDA differentiates between existing and novel risks. For example, an "adverse outcome" linked to a health complication that is known to sometimes occur with embryo transfer is more acceptable than an "adverse outcome" triggered by some complication unique to cloning.

The risk management plan acknowledges areas of scientific uncertainty and points out that cloning technology is rapidly evolving. The FDA states that emerging cloning technologies might raise risks different from current techniques.

In the notice, the FDA also announced the availability of, and requested comments on, a proposed risk management plan for animal clones and their progeny. The proposed risk management plan takes into account the risks identified in the draft risk assessment and establishes proposed measures that FDA might use to manage those risks. With a few narrow exceptions, the risk management plan simply states, for all intents and purposes, "Enjoy your cloned meat and milk!"

In addition, the FDA announced the availability of draft guidance for industry, open for public comment. This draft guidance describes FDA's recommendations regarding the use of edible products from animal clones and their progeny in human food or in animal feed. The "Guidance to Industry" document is less than two pages, with most of the text describing the overall process used by FDA to evaluate risks from cloned animals. Its substance appears in four paragraphs that begin with the statement – "No unique risks for human consumption were identified in cattle, swine, or goat clones." Because of the lack of applicable science, the FDA recommends that, "edible products from sheep clones not be introduced into the human food supply."

Industry is reminded in the guidance document that edible products from clones must meet all applicable federal and state food safety laws.

In its report, the FDA has acknowledged that, even if two animals have identical genes, the animals can turn out differently if their genes are turned on or off at different times, or are sequenced differently from the original sequence. These unpredictable genetic variations are linked to the high failure rate of cloned animals. (Only about 4 to 7% of cloned animals survive.) Many clones die during gestation or shortly after birth, while some are born with deformed heads or limbs or problems with their hearts, lungs or other organs.

In its report, the FDA admits animal health problems, by stating that "some animals involved in the cloning process (i.e., cattle and sheep surrogate dams, and some clones) are at increased risk of adverse health outcomes relative

to conventional animals." "Cows and ewes used as surrogate dams for SCNT-derived pregnancies appear to be at increased risk of late gestational complications" and "There is an increased risk of mortality and morbidity in perinatal calf and lamb clones."

The most severe errors in reprogramming will result in death, obvious malformations, or metabolic derangements, and are reflected in the low "success rate" of cloning, the perinatal difficulties observed in some newborn clones, and occasional examples of altered metabolic pathways in very young animals.

Can Cloned Meat and Dairy Products Be Sold as Organic?

Animal cloning is not allowed for organic production under the NOP for several reasons. An initial technical step in animal cloning is cell fusion, a process involving the transfer of DNA from one cell to another. Cell fusion is an "excluded method" in organic production under the National Organic Program (NOP) regulation.

Cell fusion, and hence cloning based on it, narrows the gene base, while organic production relies on maintenance of a broad and diverse gene pool. A species with a broad and deep gene pool is better positioned to adapt to new disease threats and environmental changes.

In addition, cloning is dependent on the use of artificial hormones to induce labor of surrogate dams. The use of artificial hormones to induce labor is prohibited in organic agriculture.

In the draft risk assessment, the FDA acknowledges a variety of animal health problems both with clones, especially in the first days and weeks of life, and the surrogate mothers required to bring them to term. For example, FDA concluded that, "Cows and ewes used as surrogate dams for SCNT-derived pregnancies appear to be at increased risk of late gestational complications."

The NOP regulation requires organic livestock producers to establish and maintain animal husbandry systems that allow natural behaviors, including those involved in reproduction, and promote the health and well-being of the animals. Breeding practices like SCNT cloning that result in "adverse health outcomes," "increased risks of late gestation complications," and "increased risks of mortality and morbidity" do not meet the NOP's proactive health care requirements.

Unlabeled Clones and the Organic Market

The FDA has not ruled on whether or not cloned animals and their products will need to be tracked and labeled in the human food supply and for animal feed and pet food uses. Labeling is essential in order to:

- Prevent entry of cloned animals, their progeny, and products into the organic food system;
- Protect organic livestock producers from financial losses associated with the accidental introduction of cloned animals into the organic herd;
- Conduct long-term studies on effects on human and animal health;
- Sustain consumer confidence in the food system;
- Respect consumers' right to know about the foods they consume; and
- Protect conventional livestock producers not using cloning technology from likely negative economic impacts.

A Fundamental Flaw

The FDA report states, "The Center assumes that if clones were to pose food consumption risks, the only mechanism by which those risks could arise would be from inappropriate epigenetic reprogramming…" The draft assessment states that animal clones can develop with apparently normal functions, but with subtle sub-clinical physiological anomalies, which can "…include alterations in key proteins affecting the nutritional content of food and leading to dietary imbalances." It also acknowledges that many cloned animals die during gestation or develop abnormally due to a misarranged genetic code. Despite these potential risks, the FDA assumes that existing federal and state meat inspection laws will prevent abnormal clones from entering the human food supply because they will clearly be sick or different from normal animals.

Clones that are "virtually indistinguishable" from normal progeny may enter the food supply. Sick and malformed clones may be rendered and enter the food supply indirectly via animal feed, or may find their way into pet food.

The concept of cloned animals and their products being “virtually indistinguishable” to animals resulting from natural breeding is similar to the doctrine of “substantial equivalence,” used in the 1990s by the FDA to justify approval of genetically engineered plants. “Virtually indistinguishable” is not a scientific standard. The FDA acknowledges that cloned animals that are “virtually indistinguishable” to the human eye might be different in ways that impact food safety or nutritional quality. The public is not likely to accept similarity of appearance as the decisive food safety hurdle standing between animal clones and the American food supply.

Who Gains from Unregulated and Unlabeled Cloning?

The presence in the marketplace of unregulated and unlabeled meat and milk from cloned animals will help further differentiate organic products from unsegregated conventional livestock products. This will almost certainly increase demand for organic meat and animal products.

Corporations who control the technology and proprietary strains of cloned animals will likely profit if farmers are not concerned about the risk of market rejection.

The absence of tracking or labeling protects technology companies and users of cloned animals from liability. Without traceability, it will be difficult, if not impossible, to link consumption of cloned animal products to adverse impacts on human health.

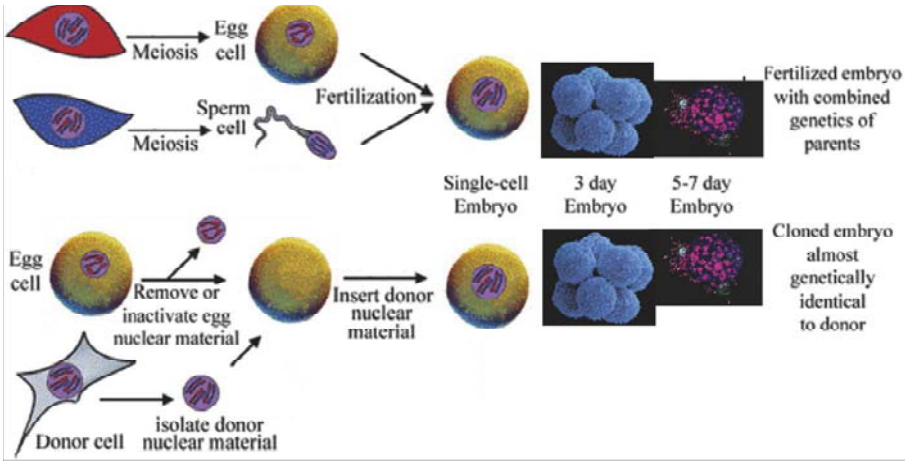
No other country has approved food from cloned animals. The introduction of cloning has the potential to seriously diminish consumer confidence in U.S. animal products and will likely depress domestic and export markets for conventional livestock products. Export sales of organic livestock products will almost certainly grow at an accelerated rate.

A December 2006 poll by the Pew Initiative on Food and Biotechnology found that 64 percent of consumers said they were uncomfortable with animal cloning, with 46 percent saying they were “strongly uncomfortable.” Other polls have shown comparable levels of consumer reticence. As consumers learn more about the risks associated with animal cloning, it is hard to imagine a softening of consumer anxiety over cloning. For this reason, a comprehensive economic impact analysis should be conducted to examine the impacts of cloning technology on existing markets for conventional and organic livestock products.

II. A Brief History and Description of Cloning Methods and Technology

Since the beginnings of animal agriculture, humans have selected and propagated animals that have traits that humans find desirable, such as fewer health problems, higher rates of feed efficiency, or superior end products. Various breeding techniques, as described below, have been developed to aid in the selection and propagation processes. This section draws heavily on the content of Chapter 2 of the FDA risk assessment, which is entitled "Technology Overview Somatic Cell Nuclear Transfer and Other Assisted Reproductive Technologies."

Natural Breeding - Traditionally, selected sires and dams have been mated using natural breeding methods, where the male copulates with the female, ejaculating sperm to fertilize an egg or eggs, resulting in offspring with genetic material from both parents.



This form of reproduction is limited by species-specific characteristics such as average litter size, frequency of estrus, and gestation length of the female, and, for the male, the degree of proximity to fertile females and the ability to inseminate females with a sufficient number of normal sperm.

To help overcome some of these restrictions, various forms of "assisted reproductive technologies" (ARTs) have been adopted in animal agriculture. Artificial insemination, where sperm is collected from a selected male and placed, by human intervention, in a receptive female, has been used for several hundred years. Assisted reproductive technologies form a continuum that ranges from minimal assistance provided to animals engaged in natural service through those that rely on significant *in vitro* manipulation, such as *in vitro* fertilization and embryo splitting, to the more recent development of somatic cell nuclear transfer (SCNT), or what is colloquially referred to as "cloning."

The FDA risk assessment, risk management plan, and guidance to industry refer only to clones developed using somatic cell nuclear transfer. The agency acknowledges at several places in these documents that as cloning technologies change, additional risk issues may arise and will need evaluation.

In the U.S. dairy industry, most reproduction involves artificial insemination or some technology-enhanced intervention, and swine producers rarely use natural mating. In the beef industry, however, most reproduction occurs by natural service, and most of the world's sheep and goat production depends on natural mating.

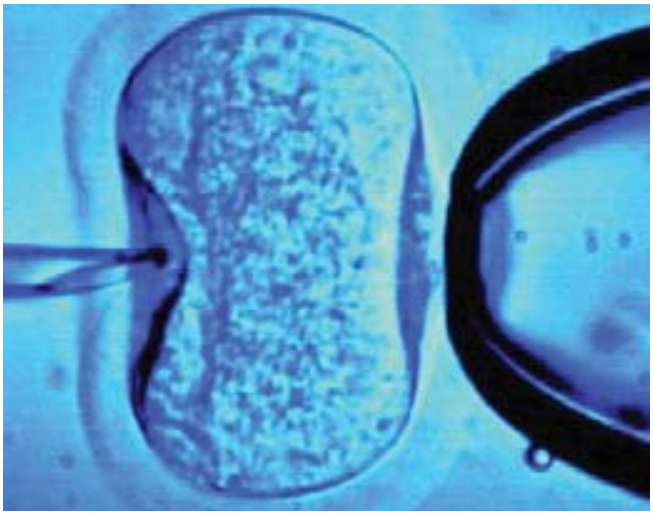
Artificial Insemination - The first ART developed was artificial insemination (AI), which is an important technique for the genetic improvement of animals, as a few select males can produce sufficient sperm to inseminate thousands of females per year, while natural service would provide for the insemination of only a fraction of those animals. Reports of AI in horses as part of breeding programs have been traced to the Arabian Peninsula in the 14th century (Bearden and Fuquay 2000). In 1899, the Russian Czar Nicholas II commissioned I.I. Ivanov to develop an AI program for horses. Although there are several methods for collecting semen, most involve training males to ejaculate into an artificial vagina. Semen is then diluted to maximize the number of services that one male can provide. The diluting solution contains factors that help to stabilize and preserve the sperm, as well as antibiotics to inhibit bacterial growth and reduce the danger of spreading any potential disease to females serviced via AI. Most collected semen is stored in glass ampoules or plastic straws, and is generally stored either in dry ice and alcohol (-100F) or liquid nitrogen (-320F). (For more detail, see the section on artificial insemination in the FDA risk assessment).

The most common AI technique employed today for dairy cows involves the use of sterile, disposable catheters that are inserted vaginally and extended through the cervix into the body of the uterus of the recipient cow (whose estrous cycle has been documented). Thawed semen is warmed to the appropriate temperature, and sperm are deposited in the uterine/cervical regions.

The primary advantages of AI to farmers include the ability to use semen from bulls anywhere in the world, and thus introduce desired genetic traits. It also allows the farmer to use multiple sires in a herd without the costs of maintaining animals that are often difficult to handle. AI also avoids the potential physical risks to either sire or dam as part of the mating process. When using AI, just as with natural breeding, care needs to be taken not to rely excessively on a few sires so as not to reduce the genetic diversity of the herd.

Most organic dairy farmers rely on artificial insemination to roughly the same degree as conventional dairy farmers.

In Vitro Fertilization - In vitro fertilization (IVF) allows for the production of offspring from animals where other ART methods fail due to difficulties with either the female (blocked oviducts, non-responsive ovaries) or male (marginal semen quality and/or quantity), or where disease is present. In cattle, it is also used for the production of embryos from sexed semen because of the low



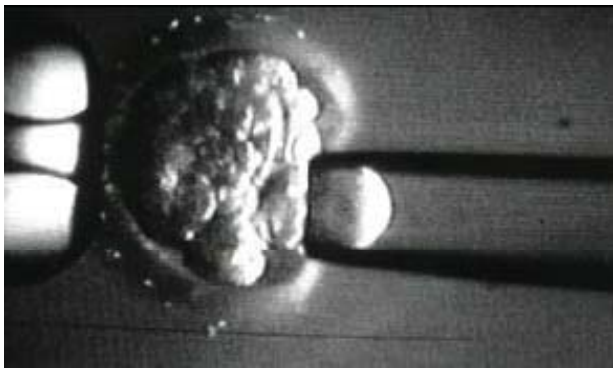
sperm counts resulting from current sexing protocols, and for the further extension of the semen of superior sires due to the relatively low level of sperm required for in vitro fertilization.

The overall technique for IVF is similar among species, and involves significant manipulations *in vitro*, or outside the body of animals. In livestock species, oöcytes (a cell that is the immediate precursor of a mature egg) are collected from the ovaries of either living or deceased animals. Ovaries can be obtained by transvaginal aspiration from live animals, or from a deceased animal at time of slaughter. Slaughterhouse ovaries are cross-sectioned and the contents of all of the follicles are collected; mature oöcytes are collected, evaluated for quality, and used for fertilization. Immature oöcytes must be allowed to continue to develop in a maturation medium. Either fresh or frozen-thawed semen can be used for fertilization. Sperm need to be capacitated *in vitro* to undergo the same maturation process that they would normally undergo in the female reproductive tract, in order to penetrate the *zona pellucida* (the clear layer of protein surrounding the oöcyte and fertilized ovum) and fuse with the ovum. *In vitro* capacitation is accomplished by placing sperm in a

medium designed to simulate the female reproductive tract and allowing the sperm to incubate in it for a period of time. Sperm are then added to ova, incubated for approximately 8-22 hours, and the resulting fertilized ova, called zygotes, are washed, examined for appropriate development, and allowed to continue to divide for up to seven days in culture. At that time, if embryos appear normal, they may be frozen for future use or inserted into the uterus of a reproductively competent female.

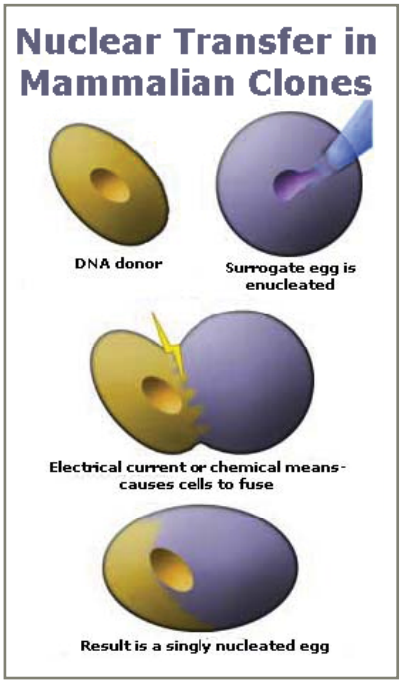
Embryo Transfer - It is possible to flush large numbers of viable embryos from a "superovulated" cow or other female animal. Superovulation of the donor animal is generally accomplished by injecting the animal with follicle stimulating hormone or other exogenous gonadotropins before she enters estrus. The hormones induce production of a large quantity of ovarian follicles containing mature, preovulatory oöcytes. Insemination is performed at appropriate times relative to ovulation, depending on the species and breed. Recipient surrogate mothers are synchronized in parallel with the donor to be ready to accept embryos for implantation and gestation. When embryos are about a week old, they are flushed out of the donor dam's uterus, isolated from the flushing solution, and examined microscopically to determine whether they are of sufficient quality to implant. If they meet the criteria for further use, embryos can be transferred immediately to a waiting synchronized recipient animal, frozen for later use, or split into halves (see embryo splitting discussion below). Fresh or thawed embryos are inserted into surrogate mothers, where they attach to the lining of the uterus, and progress through the normal course of pregnancy.

Embryo Splitting - Genetically identical individuals derived from a sole embryonic source can arise naturally, as in the case of spontaneous monozygotic twins, or *in vitro* via the manual splitting of early stage embryos. Embryo splitting may be considered the first true "cloning" procedure involving human intervention, and was first described by Willadsen and Polge in 1981, when monozygotic twin calves were produced. Embryo splitting can be used in very early embryos. Briefly, two-cell embryos derived from either *in vitro* fertilization, or embryo rescue following *in vivo* fertilization (as described for embryo transfer) are held in place with micropipettes under a microscope. The zona pellucida of these embryos is opened, and the two-celled embryo is then split into individual cells with a finely drawn needle or pipette. One of the cells is left in the original *zona pellucida* and the other is either placed into an empty *zona pellucida* or allowed to develop without a *zona pellucida*. These so-called demi-embryos can be cultured *in vitro* for a few days, inspected for appropriate growth, and then transferred directly to synchronized recipient dams, or frozen for future use.



Blastomere Nuclear Transfer (BNT) - The next evolution of assisted reproductive technology involves fusion with an enucleated oöcyte, where the nucleus has been removed. This method expands on the embryo splitting procedure described previously by allowing the use of cells from later stage embryos. In BNT, embryos of the eight to sixteen-cell stage, compact morulae, and the inner cell mass from blastocysts can be used as donor nuclei (First and Prather 1991). Fusion of these later stage blastomere cells with enucleated oöcytes reprograms the blastomere nuclei to allow them to develop as zygotes. Blastomeres from bovine embryos up to the 64-cell stage can be

fused with enucleated freshly fertilized oöcytes and cultured to develop into genetically identical individuals (Keefer et al. 1994). Cell nuclei derived from the inner cell mass of expanded blastocysts transferred into enucleated host cells are also capable of development resulting in offspring (Sims and First 1994).



Somatic Cell Nuclear Transfer (SCNT) - Somatic cell nuclear transfer, commonly referred to as "cloning," is another process by which animals are reproduced asexually. In SCNT, a differentiated somatic cell (a non-germ line cell from an existing animal) is introduced to an oöcyte that has had its nucleus (and thus its genome)[1] removed, and then, following some manipulations, is induced to start replicating. If all goes well, the dividing cell is implanted into a female animal (surrogate dam), where it continues to develop into a fetus.

SCNT, which is the sole subject of the FDA's draft risk assessment, is a relatively new technology described by many as complex, technically demanding, and inefficient. As such, there is no set "method" that is universally employed. For species in which the cloning process has been relatively well developed, the first step is to identify the animal to use as a nuclear donor. Animals are generally selected because they have been shown to be genetically superior to herd mates for the trait(s) to be propagated. Somatic cells can be collected from the ear (hole punch) or skin (surgical incision or needle aspiration), although many other cell sources have been used. Some researchers have found that cells that are not actively dividing make the best donors, while others have found that are actively dividing cells make good donors. Some laboratories use cells from embryos or fetuses, while others use cells from aged or even deceased animals.

Once a cell has been isolated from culture, either the entire cell or just its nucleus is transferred under the *zona pellucida* of the enucleated oöcyte using a very thin glass micropipette to await fusion (Solter 2000). The enucleated oöcyte contains all of the nonnuclear cellular components required for the early development of an embryo.

In order to begin the development process, the membranes separating the oöplast and the donor nucleus (or cell) must be fused. This can be accomplished in two ways: (1) by the administration of a brief electrical pulse, or (2) chemical fusion. Electrical stimulation appears to be the more commonly used technique and involves the application of one to several micro-bursts of a mild electrical current in the vicinity of the cells. This induces the formation of pores between the somatic donor cell and oöplast, which functionally makes the two cells one. This process also stimulates embryonic development, which if successful, results in the development of blastocysts that are transplanted into surrogate mothers.

Identical Twins vs Clones - Identical twins, also called *monozygotic twins*, originate from a single zygote, or fertilized egg. DNA from the father combines with DNA from the mother in the nucleus of the zygote. A new diploid genome is created by the fusion of two haploid genomes. Once the zygote has undergone the first division (or cleavage), it is referred to as an embryo. In the case of twins, early in pregnancy, the zygote divides into two parts. The two parts develop into separate individuals who have the same genetic markup.

Twins are formed through the union of egg and sperm carrying DNA from male and females animals. The DNA mixes, and then the cells divide. A clone, on the other hand, is the result of asexual reproduction, and carries the DNA of a single living or dead male or female, but not both.

Epigenetic Reprogramming - Genetic reprogramming is the process of altering the gene expression pattern associated with the differentiated, donor cell to one that is appropriate for early embryonic development. Donor cells tend to be specialists. That is, they have differentiated to such

a degree that their genomes have been "reconfigured" in ways that are, as yet, not fully understood, in order to carry out the particular function for which they have been destined by their particular developmental fate. Kidney cells, for example, do not transcribe the milk producing instructions of the mammary gland, yet they continue to carry those genes. In order for cloning to be successful, donor cells must be "reprogrammed" to express the full set of instructions contained in the genome such that "normal" development of an embryo can occur.

Dolly 1996 - 2003
The first cloned mammal. Inefficient reprogramming of epigenetic marks is the main reason for the poor health of cloned animals.

Mammalian embryos naturally experience major epigenetic reprogramming primarily at two times in their development, both of which have significant implications for cloning. One of these takes place soon after fertilization, and is referred to as preimplantation reprogramming; the other occurs during gametogenesis (the development of cells that ultimately become the sperm and egg). Because preimplantation reprogramming occurs after fertilization, and in the case of nuclear transfer, after fusion of the donor nucleus with the oöplast, it is the most immediately affected by the cloning process, and may be most directly implicated in the development of clones with defects. Gametogenic reprogramming may also be involved in the abnormalities noted in clones, but it likely has more far-reaching implications for progeny, because it generates the gametes used for the sexual reproduction of clones.

In the process of cloning, the donor nucleus must be coaxed to direct embryonic development as if it were a fertilization-derived zygote. Most of the time this is not successful. Anomalous epigenetic reprogramming is observed at the global genomic and individual gene level in clone embryos and fetuses, and in similar developmental stages of animals produced using ARTs with significant *in vitro* culturing components. Many of these are lethal, as demonstrated by the low success rate of IVF and the even lower success rate of SCNT. In the small number of successful cases that ultimately result in normal-appearing and functioning animals, SCNT-derived embryos appear to be able to carry out reprogramming just about as well as fertilization-derived embryos. Live and apparently healthy clones, however, may exhibit some level of epigenetic differences relative to fertilization-derived animals.

Biologists are just beginning to understand the highly complex interactions that must occur to choreograph the millions of molecular interactions that signal the expression or silencing of genes in a particular cell or at any point in its life cycle. Although some clones may develop into healthy animals, the low success rate of SCNT is likely associated with the inability of clones to reprogram the somatic nucleus of the donor to the state of a fertilized zygote. In fact, gene expression analyses and extensive phenotypic characterization of cloned animals suggest that most, if not all, clones suffer from at least subtle abnormalities.[2] Research data imply that even apparently normal cloned animals may have subtle abnormalities in gene expression.[3] Humphreys, et al, reports, "Our results demonstrate frequent abnormal gene expression in clones, in which most expression abnormalities appear common to the nuclear transfer (NT) procedure whereas others appear to reflect the particular donor nucleus."[4]

The most severe errors in reprogramming will result in death, obvious malformations, or metabolic derangements, and are reflected in the low "success rate" of cloning, the perinatal difficulties observed in some newborn clones, and occasional examples of altered metabolic pathways in very young animals.

Even a fully functional reprogrammed genome may have been subjected to some epigenetic alterations. Bringing nuclear transfer to routine practice requires greater knowledge and understanding of the basic biological processes underlying epigenetic controls of nuclear activities. An important issue at present is to limit the production of those aberrant phenotypes that may result in significant insult to the nature and welfare of animals.[5]

As reported by Wilmut in 2006, “This literature survey shows that clone developmental abnormalities, variation among clones, and variation between clone and parent are prevalent at most stages of development (cleavage, placental, fetal, neonatal, maturity), and that occasionally the observed variation greatly exceeds that which might be expected.”[6]

Given its current high costs (approximately $20,000 for a live calf) and relatively low success rates (< 10 percent), SCNT will likely be used primarily to improve production characteristics of food producing animals by providing breeding animals, just as any breeding program would select the most elite animals for breeding, and not as production animals.

III. What the FDA has Proposed

According to the Draft Risk Assessment, FDA's role in performing the risk assessment was to determine whether cloning poses any risk to animals involved in the cloning process, and whether the consumption of food products from clones or their progeny poses any additional risk compared with food from conventionally produced animals.

In its Guidance to Industry, the FDA states, "The Draft Risk Assessment did not identify any unique risks for human food from cattle, swine, or goat clones. Therefore, there is no science-based reason to recommend any additional safeguards. As such, we do not have any recommendations for any additional measures related to the use of products from cattle, swine, or goat clones as human food."[7]

In other words, the FDA proposes that the meat and milk from clones and from the progeny of clones be allowed for human and/or livestock consumption without further testing or labeling.

Submitting Comments to the FDA

Draft Risk Assessment documents are available for public comment for 90 days (through April 2, 2007). Comments should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments may also be submitted electronically at http://www.accessdata.fda.gov/scripts/oc/dockets/comments/getDocketInfo.cfm?EC_DOCUMENT_ID=1369&SORT=START&MAXROWS=15&START=151&CID=&AGENCY=FDA

Written comments should be identifi ed with the docket number found in the heading of the document. For convenience in reviewing the comments, FDA requests that comments be separately identified as to whether they apply to the Draft Risk Assessment (Docket No. 2003N-0573), the Proposed Risk Management Plan (Docket No. 2003N-0572), or Draft Guidance for Industry (Guideline No. 179, Docket No. 2003N-0573).

IV. Impacts of Cloning on Animal Health and Reproduction

Nuclear transfer (NT), at present, is an inefficient process: in cattle, only around 6% of the embryos transferred to the reproductive tracts of recipient cows result in healthy, long-term surviving clones. Of concern are the high losses throughout gestation, during birth and in the post-natal period through to adulthood. Many of the pregnancy losses relate to failure of the placenta to develop and function correctly. Placental dysfunction may also have an adverse influence on postnatal health. These anomalies are probably due to incorrect epigenetic reprogramming of the donor genome following NT, leading to inappropriate patterns of gene expression during the development of clones.[8]

As reported by the FDA, SCNT is a biologically imprecise and inefficient process resulting in few live births relative to the number of implanted embryos, and that some animals are born with obvious defects or subtle anomalies. Panarace et al conducted research to summarize 5 years of commercial experience with cloning in three countries (United States, Argentina and Brazil). Overall, only 9% of transferred embryos resulted in calves; efficiency ranged from 0 to 45% (most were from 1 to 10%, but 24% of cell lines never produced live calves).[9]

SCNT, like the other newer forms of ARTs (e.g., in vitro fertilization, embryo splitting) results in some known adverse outcomes to the animals and possibly the dams bearing those pregnancies.[10] Unlike other forms of ARTs, however, SCNT pregnancy losses occur at all stages of gestation in cattle.

The Draft Risk Assessment compares SCNT with other ARTs with respect to effects on animal health and concludes that some animals involved in the cloning process (i.e., cattle and sheep surrogate dams, and some clones) are at increased risk of adverse health outcomes relative to conventional animals. Cows and ewes used as surrogate dams for SCNT-derived pregnancies appear to be at increased risk of late gestational complications such as hydrops, as well as dystocia at parturition, that occur at a lower frequency with other ARTs that have a significant *in vitro* culturing component. Surrogate swine and goat dams bearing clones do not appear to be at increased risk. There is an increased risk of mortality and morbidity in perinatal calf and lamb clones compared with calves and lambs produced using other ARTs. In cattle and sheep, the increased risk appears to be related to large offspring syndrome.

Hydrops - Clone pregnancies have been lost during the second and third trimesters and have been accompanied by reports of hydrops (abnormal fluid accumulation in one or more compartments of the placenta and/or the fetus itself), enlarged umbilicus, and abnormal placenta (Batchelder, 2005). A recent study by Wells et al. (2003) reported a high rate of pregnancy loss of non-transgenic bovine fetal fibroblast clones after

120 days gestation, with hydrops cited as the cause of pregnancy loss in 86 percent (18/21 losses) of the cases. In SCNT, incomplete or improper epigenetic reprogramming and subsequent inappropriate gene expression may be an important factor in placental development and hydrops.

Dystocia - Dystocia, or difficult labor, is an identified hazard for any pregnancy that goes to term. USDA estimates the mean dystocia risk in the general cattle population at 4 percent of pregnancies (USDA/NAHMS 1997). Rates of dystocia in surrogate dams carrying clone pregnancies are difficult to determine as clone producers have often elected to deliver clones via planned C-section as part of their animal care protocol.

Neonatal death rates for cattle clones currently average approximately 20 percent. Dystocia may be the most influential factor on calf mortality, due to trauma of difficult labor and emergency C-section; however, abnormal organ and musculoskeletal development also appear to play important roles.

Large Offspring Syndrome (LOS) - One set of reported adverse outcomes following transfer of embryos from cloning or in vitro production systems is often referred to as Large Offspring Syndrome (LOS). These include lowered pregnancy rates, increased rates of abortion, production of oversized calves, musculoskeletal deformities and disproportionalities, as well as hydroallantois (abnormal accumulation of fluid in the placenta) and other abnormalities of placental development. Clones exhibiting LOS may require additional supportive care at birth, but can recover and mature into normal, healthy animals. LOS fetuses tend to have longer than usual gestation lengths, and often labor in the dams must be induced followed by Caesarian section deliveries. The newborns tend to be large for their breeds, and often have abnormal or poorly developed lungs, hearts, or other affected internal organs (liver and kidney), which makes it difficult for them to breathe or maintain normal circulation and metabolism. LOS newborns may appear to be edematous (fluid filled), and if they are to survive, often require significant veterinary intervention. Problems have also been noted in muscle and skeletal development of animals with LOS. These animals also often have difficulty regulating body temperature.

Recent studies in which IVP and SCNT embryos were produced under the same culture conditions reported considerably higher incidences of LOS in fetal and adult cell SCNT-derived calves compared to IVP (Heyman et al. 2002; Chavatte-Palmer et al. 2002; Matsuzaki and Shiga 2002), indicating that culture conditions may not be the only factor influencing the development of LOS in cattle clones. One possible explanation for this increase in abnormalities is incomplete epigenetic reprogramming.

Calves exhibiting LOS may also show prolonged time to stand and poor or late-developing suckling behavior (Chavatte-Palmer et al. 2002; Pace et al. 2002; Batchelder 2005). Poor suckling may preclude immune transfer in colostrum-dependent species, resulting in decreased ability to respond to immune challenges.

Other abnormalities reported to coincide with LOS include respiratory, cardiac, hepatic, renal, umbilical, and immunologic problems, and may occur even among animals with birth weights within the normal range for their breed. These abnormalities may result from dysregulation of developmentally important genes rather than the uterine environment. Systemic abnormalities including organ dysfunction result in morbidity and often result in high mortality. Pulmonary abnormalities include immature lung development, insufficient lung surfactant, and failure of the lungs to inflate. Cardiovascular abnormalities include patent ductus arteriosus and ventricular defects.

Neonatal Death - In the general population of cattle and sheep, neonatal death rates are typically low. Overall, the estimated death rate of beef calves within 24 hours of birth (including stillbirths) is 3.4 percent (USDA/NAHMS, 1997). Early reports, beginning in 1998, of clone mortality rates were 50 to 80 percent (reviewed by Solter 2000). Survival rates have improved in some recent studies, with mortality during the first month of life of approximately 18 percent (21/117; Pace et al. 2002 for a cohort of mixed transgenic and non-transgenic clones) and 20 percent (6/30; Lanza et al. 2001 for a cohort of transgenic cattle), with most of the deaths occurring during the first 48 hours postpartum. Similarly, data supplied by Cyagra, Inc. to the FDA indicate 22 percent mortality in the first 48 hours (30/134) among non-transgenic clone calves born between 2001 and 2003.

In a later study, (Chavatte-Palmer et al. 2004), an additional cohort of 58 live-born clone calves were followed through maturity. Clone survival after the first week following birth was 76 percent (44/58). Clinical signs and necropsy findings for nine clones that died during the perinatal period included hyperthermia, umbilical hernia, respiratory problems, ascites (abnormal fluid accumulation) in the chest and abdomen, fatty liver, limb deformities, various digestive tract problems, and abnormal or degenerating kidneys.

Of the 134 clone calves in the Cyagra cohort, 11 were stillborn. Fifty-five additional calves that were not oversized at birth, or for which birth weights were not available, showed clinical signs often associated with LOS. The most common clinical sign was umbilical problems (41 cases), followed by tendon contracture (15 cases), ranging from mild to severe. There were also four animals with respiratory signs, five with cardio-vascular signs, three with thermoregulatory problems, two with renal or nephric signs, and five animals listed as having "abnormal development."

Musculoskeletal Abnormalities - In a long term study of health and survival of clones and their offspring, Wells et al. (2004) stated that the most common cause of mortality (either by natural death or euthanasia) of young clones at their facility was musculoskeletal abnormalities (severe tendon contracture and chronic lameness). They also reported two cases of death due to bloat, and an unspecified number of clones dying due to endophyte toxicity. Gastrointestinal problems, including bloat, have been reported in other studies (Cyagra 2003; Batchelder 2005), but can also result from poor feeding/grazing management in conventional cattle. Endophyte toxicity results from grazing fungus-infected grass by cattle sensitive to the toxin. Wells et al. acknowledge that this trait is inherited in certain lines of cattle, and likely was related to the genetics of the nuclear donor. (The clones affected by this toxicity were derived from the same donor.) Other causes of death among clones (besides those attributed to accident or management problems) included anemia, chronic heart failure, and degenerative nephrosis.

Chavatte-Palmer et al. (2004) reported that 38 of 44 clones surviving the perinatal period lived to six months of age. The authors reported an additional four clones with thymic aplasia or atrophy (underdeveloped or degenerating thymus gland) since the first report of a clone with this condition (Renard et al. 1999). On necropsy, the thymus glands of these calves exhibited abnormal tissue organization, suggesting epigenetic errors. Three calves in this group died suddenly with few or no clinical signs: two died following the onset of diarrhea and one calf died without any apparent cause. Another calf was diagnosed with diabetes insipidus.

Umbilical Problems - Of the six calves surviving the neonatal period in the Batchelder (2005) study, three more calves died or were euthanized during the juvenile period. Two calves died due to complications involving a non-healing umbilical stalk and patent urachus. Another calf died of apparent pneumonia, and was diagnosed with cardiac abnormalities and pulmonary hypertension upon necropsy. Two of the calves exhibited neurological signs, including head twitching and seizures. Three clones (Holstein breed) and all nine comparators survived the juvenile period.

Health issues observed in some of the Cyagra clones included an increased incidence of umbilical problems (enlargements, excessive bleeding, navel infection), contracted tendons, and cryptorchidism (a condition in which one or both testicles are retained in the body cavity). All of these conditions are seen in sexually derived animals, but at lower frequencies than in clones.

Long-term Survival - Wells et al. (2004) conducted a retrospective analysis of cattle clones that were generated through SCNT at AgResearch in New Zealand to determine their long-term survival. They found that 133 (13 percent) calves were born from 988 SCNT embryos transferred into recipient cows. Sixty seven percent of these calves (89 animal clones) survived to weaning (3 months of age) and 81 percent of the calves (72 animal clones) survived post-weaning. The reasons for death were variable, including euthanasia due to musculoskeletal abnormalities (4 animals), bloat (2 animals), ryegrass staggers (2 animals), misadventure (2 animals) and one case each of anemia, heart failure, kidney failure, ruminal acidosis, lungworm, clostridia, and overfeeding on grain supplement.

The lifespan of mice cloned from somatic cells is significantly shorter than that of genotype- and

sex-matched controls, most likely due to severe pneumonia and hepatic failure.[11]

Animal Behavior - Based on a series of studies evaluating approach to other animals and novel objects, clones exhibited age-appropriate behaviors, but were reported to be more aggressive and inquisitive than controls, and spent more time grooming and socializing. Clones tended to spend less time in playful behavior than controls. Review of records on the cow that served as the nuclear donor for the clones indicated that she had displayed similarly aggressive and inquisitive behavior as a young animal, suggesting that at least some of these behavioral traits may be genetically controlled. Clones spent more time in proximity to adult animals in an adjacent pen (which also housed the nuclear donor), and in proximity to the feed bunk compared to control animals. In general, clones were reported to spend more time with each other rather than socializing with control animals. The authors speculated as to whether clones exhibit genetic kinship recognition. Batchelder (2005) reported aggressive feeding behavior and "insatiable" appetites among eight juvenile clones, as well as increased water consumption.

Swine - Swine are the most recent of the livestock animal species considered in the FDA's assessment to be cloned. In general, success rates from the studies evaluated (as measured by number of viable offspring) are low even when compared to reports of cloning in other species. Most pregnancies fail to reach term. Swine carrying clone pregnancies do not appear to experience hydrops and dystocia, however. Park et al. (2004a and 2005) reported the death of 22 of 35 live-born SCNT hog clones within the first week of life. Several health problems were noted including cerebromeningitis, diarrhea, leg abnormalities, Leydig cell hypoplasia, and unknown factors.

In the Viagen dataset, hog clones weighed less at slaughter and took 27 days longer to reach slaughter weight than their contemporary comparators. Three clones were described as "poor-doers:" animals that exhibited slow growth rates and other health problems. All three of these animals suffered from periodic or chronic scouring along with other health problems. On average, organ weights as a percentage of body weight were lighter for clones than for comparators. Overall, swine clones had lower IGF-I and estradiol-17 levels at slaughter compared to non-clone comparators. One clone was diagnosed with a lung adhesion at slaughter. During discussions with CVM, clone producers indicated that agalactia (failure to lactate) was noted in sows giving birth to piglet clones.

Sheep - As noted for cattle, abnormal development of the placenta in clones of both embryonic and somatic cell origin is one cited cause of mid- and late-term spontaneous abortion in sheep (Wells et al. 1998). In another study comparing cloning procedures with other ARTs, an increase in assisted deliveries
was observed for ewes carrying clone and IVP-derived pregnancies compared to AI or natural service pregnancies (Ptak et al. 2002). Delivery was assisted because of a lack of adequate uterine contractions and general lack of preparedness for delivery in the ewes carrying clone and IVP-derived lambs.

Ptak et al. (2002) reported that normal maternal behavior was impaired in ewes carrying both IVP and clone-derived pregnancies. Ewes carrying IVP or clone embryos did not show common signs of labor (increased activity, bleating, contractions), and delayed licking neonatal lambs (to bond with lambs, and to stimulate lambs to breathe, stand and nurse). Ptak et al. (2002) also reported a lack of expected pre-partum changes such as cervical dilation and swelling of the vulva in ewes carrying clone pregnancies. In such cases, delivery was assisted by administering hormones to induce more typical labor, or by C-section.

Studies involving IVP and cloning in sheep report lambs born with many of the same clinical signs as

noted for cattle clones, including LOS (reviewed by Young et al. 1998). Mortality rates were elevated relative to lambs produced by natural service in IVP- , BNT-, and SCNT-derived lambs (Campbell et al. 1996; Ptak et al. 2002).

Kidneys from lambs derived by nuclear transfer are frequently abnormal and are characterized by an enlarged pelvis and narrow medulla, consistent with lower urinary tract obstruction and development of variable hydronephrosis.[12]

It has been reported in the popular press and elsewhere that "Dolly," the first adult SCNT sheep, showed signs of premature arthritis (Dyer 2002), but no other reports of age related illnesses in sheep clones were found. Dolly was euthanized in early 2003 at approximately six and one half years of age having contracted a virulent form of lung disease. Recent reports in the popular press have recorded the death of a relatively young sheep clone in Australia (Arlington 2003), although the cause of death for this animal has not been reported. Under ideal conditions, sheep may live to 15 years of age.

Goats - In general, cloning-related problems similar to those noted for sheep and cattle have not been reported for goats. Because there are relatively few reports of goats bearing clone pregnancies and the number of animals involved in individual studies is small, the CVM could not determine whether the lack of complications reported in this species was the result of differences in methodology, species-specific differences, or simply an artifact of the small numbers of animals involved and small number of published papers. Data on effects on surrogate dams are not currently available. No reports on aging and maturity in goat clones were identified.

In one study, progeny from goat clones were found to have shorter telomere length in testicular biopsies compared to conventionally derived animals and the telomere lengths were intermediate to the values obtained for their clone fathers' and age-matched control testes (Betts et al. 2005). This suggests that there was incomplete telomere elongation in the offspring of clones.

FDA's Conclusions

According to the FDA's Draft Risk Assessment, the risks of cloning to animal health may be summarized as follows:

- Cows and ewes used as surrogates for SCNT derived pregnancies appear to be at increased risk (e.g., incidence) of late gestational complications such as hydrops, as well as dystocia at parturition, that occur, but at a lower frequency, with other ARTs such as IVP. The risk to surrogate swine and goats bearing clones does not appear to be ncreased compared to the general population; however, the limited dataset in these species increases the uncertainty associated with this conclusion.

- There is an increased risk (e.g., incidence) of mortality and morbidity in perinatal calf and lamb clones compared with calves and lambs produced using other ARTs. In cattle and sheep, the increased risk appears to be a function of LOS. Survival of these clones appears to be a function of both the severity of the clinical signs and neonatal management. The available information suggests that morbidity and mortality Cloning for Food The Organic Center is not increased in perinatal swine and goat clones; however, the limited dataset in these species increases the uncertainty associated with this conclusion.

- Animal clones of all of the species onsidered in the juvenile to prepubertal age cohort do not appear to be at an increased risk of morbidity or mortality compared to animals produced by natural service or ARTs. Most animals surviving the neonatal period a appear to grow and develop normally.

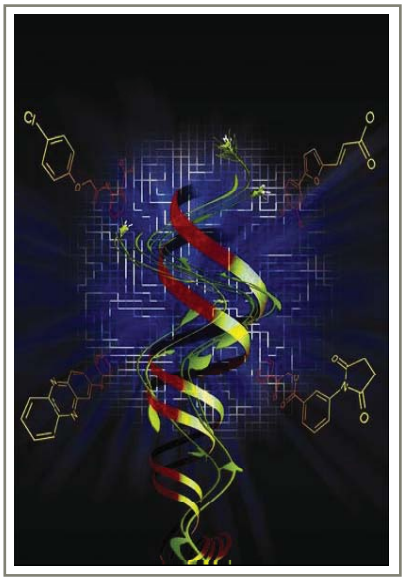
- No increased risk of adverse health effects is apparent in bovine clones approaching reproductive maturity. This conclusion should be tempered by the relatively small dataset available for analysis. There are insufficient data to assess the risk in this developmental node for swine, sheep, or goat clones.

- Insufficient data exist to assess the risk of adverse health effects to mature and aging animal clones. The available information indicates that there are no apparent risks to the health of maturing animals from cloning. Drawing empirical conclusions regarding longevity in domestic livestock clones is difficult due to the relatively short time that the technology has existed.

V. Potential Impacts of Cloning on Food Quality and Safety

The FDA's "Critical Biological Systems Approach," the framework FDA used to assess cloning food safety risks, led the agency to a key presumption. The FDA presumes that if food products from healthy animal clones and their progeny meet all local, state, and federal regulatory requirements set forth for those products (e.g., Pasteurized Milk Ordinance, 58 USDA inspection criteria, absence of drug residues), and are not materially different from products from conventionally bred animals, then they would pose no more food consumption risk(s) than corresponding products derived from conventional animals.

Following the FDA's reasoning, because animals found to have a disease or condition that would render them adulterated (e.g., unfit for consumption, unhealthful, unwholesome) are prohibited from entering the human food supply, the only remaining food consumption hazards arising from gene dysregulation would be those that allow an animal clone to develop with apparently normal functions, but with sub-clinical physiological anomalies (i.e. subtle hazards).



The primary concern for milk and meat from animal clones is that inappropriate reprogramming of the nucleus of donor cells may result in epigenetic changes creating subtle hazards that may pose food consumption risks. Because, as previously discussed, there is no a priori reason to expect that SCNT will introduce any new, potentially toxic substances into the milk or meat of otherwise healthy animals, the remaining food safety concerns addressed whether subtle changes have occurred that would alter the presence of important nutrients. The most likely dietary risk would then be the absence or significant decrease in levels of vitamins and minerals whose daily requirements are in large part met by milk or meat.

Based on the available data, FDA has concluded that milk from cow clones does not appear to differ significantly in composition from milk from non-clones. Small differences have been noted between clones and comparators, but given the different diets and husbandry conditions of these animals, it is difficult to determine with certainty whether the small changes seen in some components were a function of the diet, handling, or related to cloning.

A study by Tian and her colleagues (2005) reports the results of studies on the composition of meat from bovine SCNT clones (Tian et al. 2005). There were 12 instances where the clones and genetic comparators showed differences:

- Amount of mesentery fat
- Proportion of longissimus thoracis muscle over body weight
- Muscle moisture
- Amount of crude protein in the semitendinosus muscle
- Amount of linolenic acid in the kidney leaf fat
- Amount of linolenic acid in the longissimus thoracis
- Amount of linolenic acid in the semitendinosus muscles
- Amount of oleic acid in the semitendinosus muscle
- Amount of palmitic acid in the semitendinosus muscle
- Amount of linoleic acid in the semitendinosus muscle

All of the parameters were higher in the clones than in the genetic or breed comparators, except for crude protein or muscle moisture in semitendinosus muscle. Despite these differences, the researchers concluded that the meat from somatic animal clones falls within normal industry standards and does not significantly differ from those of the genetic or breed comparators. The differences observed were considered due to the superior genetics of the donor bull from which the line of clones was derived.

Carcass qualitative characteristics were similar for swine clones and comparators. Differences in backfat thickness and marbling may be due to the lighter weight of clones at slaughter vs. comparators. Differences in meat nutrient composition were very small and likely not biologically relevant. No biologically relevant differences were observed in the food composition values between muscle of swine clones and comparators.

Although there is no reason to suspect that cloning will cause the synthesis of new proteins in animals that appear healthy and normal, the FDA risk assessment discusses two possible pathways that might pose an increased allergenic risk from the edible products of animal clones. One is an increase in the relative amount of an individual protein component of milk or meat that may only be present in very low or trace amounts. The other possible pathway is that processing of the proteins during their generation in the mammary gland or muscle cells somehow alters their antigenic presentation in milk. Similar risks are not likely to occur for meats, as meat allergies are so much less prevalent in the population that they are almost considered idiosyncratic, and individuals likely to suffer from meat-related allergies are likely to avoid those meats entirely.

The FDA has concluded that:

1) Edible products from perinatal bovine clones may pose some very limited human food consumption risk. The underlying biological assumption in place for this age cohort is that perinatal clones may be fragile at birth due to residual incomplete or inappropriate reprogramming of the donor nucleus. Data from both the peer-reviewed publications and Cyagra are consistent with that assumption; some perinatal clones do not survive for several reasons, including poor placentation, LOS, and in some cases, frank malformations. Postulated differences in epigenetic reprogramming between perinatal clones and comparators suggest that some subtle hazards may have been introduced into these animals. Given that perinatal clones may differ from comparator animals of the same age, at this time, the FDA concludes that they may pose a very limited nutritional risk for consumption as food. Rendering these clones, the FDA concludes, however, will not pose such risks in animal feed or to humans consuming animals fed material derived from the clones.

2) Edible products from juvenile bovine clones pose no additional food consumption risk(s) relative to corresponding products from contemporary conventional comparators. The underlying biological assumption for this developmental node is that if any anomalies were to be found in the youngest clones and those animals were to survive to be healthy adults, the juvenile developmental node would be a period of equilibration and normalization. The data appear to be consistent with such a hypothesis.

3) Edible products derived from adult bovine clones pose no additional risk(s) relative to corresponding products from contemporary conventional comparators.

4) Edible products from adult swine clones pose no additional risk(s) relative to corresponding products from contemporary conventional comparators.

5) Except by relying on underlying biological assumptions, and by inference from other species, there is insufficient information on the health status of sheep clones to draw conclusions with respect to potential risks that could be posed from the consumption of food products. There are reports of anomalies noted in fetal sheep clones that have died or been terminated, and reports on the pathology associated with animals that do not survive.

6) Edible products from goat clones pose no additional food consumption risk(s) relative to corresponding products from contemporary conventional comparators. Based on the data reviewed, there do not appear to be any anomalies present in the goat clones that would have a direct impact on the safety of food products derived from these animals. Goats appear to be relatively

"cloning friendly" with a high degree of successful live births following confirmation of pregnancy. All reports of health of the goat clones seem to indicate that they are normal and healthy.

7) Edible products derived from the progeny of clones pose no additional food consumption risk(s) relative to corresponding products from other animals. [P 296]

8) No animal feed risks unique to clones were identified in the Draft Risk Assessment. FDA therefore does not have recommendations for any additional measures related to the use of clones of any age or species for the production of feed for animals that are based on the fact that the animals are derived from cloning. This conclusion applies to rendered products from any clones and the use of milk from clones for animal feed.[13]

VI. Can Cloned Meat and Dairy Products Be Sold as Organic?

As reported by the FDA, one of the initial technical steps in animal cloning is cell fusion.[14] DNA is transferred from one cell to another. As a form of cell fusion, the practice is prohibited in organic production under the National Organic Program (NOP) regulation as an "excluded method."

Excluded methods, which are not allowed in organic production or processing, are defined as, "a variety of methods used to genetically modify organisms or influence their growth and development by means that are not possible under natural conditions or processes and are not considered compatible with organic production. Such methods include cell fusion, microencapsulation and macroencapsulation, and recombinant DNA technology (including gene deletion, gene doubling, introducing a foreign gene, and changing the positions of genes when achieved by recombinant DNA technology). Such methods do not include the use of traditional breeding, conjugation, fermentation, hybridization, in vitro fertilization, or tissue culture."[15]

Animal cloning is not allowed for organic production under the NOP for several reasons. Since cloning relies on cell fusion, it is explicitly prohibited in organic production. Clearly, cloning is not possible under natural conditions. It is not considered compatible with organic production, since cloning narrows the gene base, while organic production relies on maintenance of a broad and diverse gene pool.

In addition, cloning is dependent on the use of artificial hormones to induce labor of surrogate dams. The use of artificial hormones to induce labor is prohibited in organic agriculture.

Animal Husbandry Issues

During cloning, an animal's DNA is inserted into an egg, where the DNA has been removed. The resulting embryo is implanted into a surrogate mother, where it forms a genetically identical copy of the original animal.

But even if two animals have identical genes, they can turn out differently if those genes are turned on or off at different times, or are sequenced differently from the original sequence. These unpredictable genetic variations are linked to the high failure rate of cloned animals. Many clones die during gestation or shortly after birth, while some are born with deformed heads or limbs or problems with their hearts, lungs or other organs.[16]

In its report, the FDA admits animal health problems, by stating that "some animals involved in the cloning process (i.e., cattle and sheep surrogate dams, and some clones) are at increased risk of adverse health outcomes relative to conventional animals." "Cows and ewes used as surrogate dams for SCNT-derived pregnancies appear to be at increased risk of late gestational complications." "There is an increased risk of mortality and morbidity in perinatal calf and lamb clones."[17]

The NOP regulation requires organic livestock producers to establish and maintain preventative livestock health care practices and accommodate the health and natural behavior of the animals. Breeding practices, such as cloning, that result in "adverse health outcomes," "increased risks of late gestation complications," and "increased risks of mortality and morbidity" do not meet the NOP's proactive health care requirements.

Unlabeled Clones and the Organic Market

While the CVM report concludes that livestock products from healthy clones are likely to be safe for human consumption, the FDA has not ruled on

whether or not cloned animals and their products will need to be tracked and labeled.

At a minimum, there should be mandatory tracking and labeling of cloned animals and animal products as: Can Cloned Meat and Dairy Products Be Sold as Organic?

- The best way to prevent entry of cloned animals, their progeny, and products into the organic food system;
- The only way to conduct long-term epidemiological studies;
- The only way determine with any level of certainty the effects on human health;
- The best way to protect consumer confidence in the food system;
- The only way to protect consumers' rights to know about the foods they consume; and
- The best way to protect the interests of conventional and organic livestock producers, who are likely to suffer negative economic impacts from un-segregated products, similar to what has happened with losses related to un-segregated GMO rice.

Introduction of Experimental Technology

While cloning may prove to be a benign technology in the long run, there is no shortage of highly productive breeds and lines of livestock. There is no shortage of meat or milk in the U.S. In fact, meat and milk markets are often depressed due to over-production.

This experimental technology introduces an inherent, and often overlooked, danger – narrowing of the gene base. Biologically speaking, a species' survival is directly linked to genetic diversity. With a broad and deep gene pool, a species, whether wild or domesticated, is better positioned to adapt to new disease threats and environmental changes. For instance, a species with a narrow gene pool can collapse when animals encounter unanticipated diseases.

The FDA report states, "The Center assumes that if clones were to pose food consumption risks, the only mechanism by which those risks could arise would be from inappropriate epigenetic reprogramming…"[18]

Despite the fact that many cloned animals die during gestation or develop abnormally due to a misarranged genetic code, the FDA assumes that only those animals which appear to be healthy and normal would enter the human food chain, since they are "virtually indistinguishable." The report goes on to state that animal clones can develop with apparently normal functions, but with subtle sub-clinical physiological anomalies. "These could include alterations in key proteins affecting the nutritional content of food and leading to dietary imbalances."[19] Because these animals appear to be normal, their products would find their way into the human food supply. Tracking of cloned animals is imperative for products from animals with sub-clinical anomalies to be identified and studied.

The concept of cloned animals and their products being "virtually indistinguishable," is similar the doctrine of "substantial equivalence," used earlier by the FDA to justify the untracked and unlabeled introduction of genetically modified organisms (GMOs). It is not a scientific standard. It is not even a rational standard, since animals that are "virtually indistinguishable" to the human eye might be different in ways that impact food safety or nutritional quality. The public is not likely to accept similarity of appearance as the decisive food safety hurdle standing between animal clones and the American food supply.

Who Gains from Unregulated Cloning?

In the short-term, the presence of unregulated and unlabeled meat and milk from cloned animals will help further differentiate organic products from unsegregated conventional livestock products. This will likely result in more consumers purchasing organic products.

Corporations who control the technology and proprietary strains of cloned animals will likely profit if farmers are not concerned about the risk of market rejection.

The absence of tracking or labeling protects technology companies and users of cloned animals

from liability. Without traceability, the determination of causes of harm, should harm occur, is much more difficult to prove.

The Draft Risk Assessment does not address the potential economic effects of allowing the unregulated use of animal cloning without traceability or labeling. No other country has approved food from cloned animals. Unlabeled introduction of cloning has the potential to seriously diminish consumer confidence, further depressing domestic and export markets for conventional livestock products. Sales of organic livestock products would almost certainly grow at an accelerated rate.

A December 2006 poll by the Pew Initiative on Food and Biotechnology found that 64 percent of consumers said they were uncomfortable with animal cloning, with 46 percent saying they were "strongly uncomfortable." Likewise, an online poll conducted by the Minneapolis Star Tribune immediately after FDA's announcement found that 60% of respondents said that they would not eat food products from cloned animals.

Prior to full approval, a comprehensive economic impact analysis should be conducted to examine the technology's impacts on existing markets for conventional and organic livestock products.

Footnotes

1) The total genetic material of an organism is referred to as its "genome," and consists of long strands of DNA packaged in chromosomes.

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6) Wilmut,I. 2006. "Are there any normal clones?" Methods Mol.Biol. 348:307-318.

7) Guideline No. 179, "Guidance for Industry Use of Edible Products from Animal Clones or their Progeny for Human Food or Animal Feed" U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, CENTER FOR VETERINARY MEDICINE, December 28, 2006.

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