Animal Cloning:

Risk Management Plan for Clones and their Progeny

January 15, 2008

ADDRESSES:

1. Single copies of this Risk Management Plan are available from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855. Please enclose a self-addressed, adhesive label to assist that office in processing your request. This Risk Management Plan is also available on the Internet at: http://www.fda.gov/cvm/cloning.htm.

2. The accompanying Risk Assessment and Guidance for Industry are also available from the above address and internet site.

3. FOR FURTHER INFORMATION CONTACT: Larisa Rudenko, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-276-8245, e-mail: clones@cvm.fda.gov.

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INTRODUCTION: Risk Management is a set of activities that integrates risk assessment results with other information to make decisions about the need for and method of risk reduction (NRC 1994). Risk managers deal with broad social, economic, ethical, and political issues in choosing from a set of options, using the results of the risk assessment and their understanding of those other issues (NRC 1996). FDA risk managers consider relevant public health, scientific, and regulatory issues. The ultimate goal of risk management is to generate a set of actions that reduce or prevent risks (Presidential/Congressional Commission 1997).

This Risk Management Plan is designed to identify the relevant issues to be considered in managing risks associated with animal cloning for agricultural purposes and to present actions to manage those risks that are within FDA's purview to address. In particular, FDA addresses potential food consumption risks in the risk management plan and has published an accompanying Guidance for Industry that presents the agency's current thinking on the introduction of edible products from clones and their progeny into the animal feed and human food supply. FDA recognizes that certain of the issues related to animal cloning for agricultural purposes are not within the agency's mission. Therefore, although FDA acknowledges that all relevant issues need to be considered, some of these issues cannot be addressed within the scope of this Risk Management Plan. FDA intends to participate in other fora, as appropriate, in discussions of other issues of concern that relate to animal cloning.

BACKGROUND: In July 2001, FDA's Center for Veterinary Medicine (CVM) issued an Update on Livestock Cloning (available at http://www.fda.gov/cvm/CVM_Updates/clones.htm) and proceeded to work with stakeholders to assess potential risks presented by cloning food-producing animals. CVM also requested that companies voluntarily refrain from introducing meat or milk from animal clones or their progeny into the human or animal food supply pending completion of the risk assessment process. Among the goals of our risk assessment were the determination of whether somatic cell nuclear transfer (SCNT, the process used to produce the clones being considered in the Risk Assessment) poses any unique risks to animals involved in cloning relative to other assisted reproductive technologies (ARTs) such as artificial insemination, *in vitro* fertilization, embryo transfer, and embryo splitting, and whether foods derived from animal clones or their progeny pose consumption risks greater than those posed by foods derived from their conventional counterparts.

The total number of animals involved in agricultural cloning is likely to be quite small (a few hundreds to a few thousand) relative to the total number of domesticated animals used for food production (hundreds of millions). (For total numbers of cattle nationally, see http://www.usda.gov/nass/aggraphs/inv.htm; for swine, http://www.usda.gov/nass/aggraphs/qtr_e.htm. For animals slaughtered see

http://www.usda.gov/nass/aggraphs/caheadx1.htm for cattle and
http://www.usda.gov/nass/aggraphs/hgheadx3.htm for swine.)

The purpose of cloning is to generate animals for breeding; it is the sexually-reproduced offspring of clones that will be used for food production (Gillespie 2002). Therefore, although much of the Risk Assessment is concerned with the food consumption risks for animal clones, in reality, only a small number of clones will likely be eaten for meat, or have their milk used for human consumption. Because clones are intended as breeding stock, it is extremely unlikely that young, non-reproducing clones would be used for food.

THE RISK ASSESSMENT: The Risk Assessment specifically addresses SCNT, which allows the copying of a specific animal without sexual reproduction. This technology is evolving rapidly, and most of the current knowledge regarding SCNT comes from cattle, swine, goats, and mice. The focus of the Risk Assessment is on those domestic livestock that have been cloned, i.e., cattle, swine, sheep, and goats.

In the Risk Assessment, CVM has conducted the most comprehensive examination of the health of livestock clones to date to determine whether cloning poses risks to animals involved in the cloning process, and whether food from clones or their offspring would pose any risk to humans eating meat or drinking their milk as compared with animals bred using other assisted reproductive technologies. We performed a thorough search of the literature on clones, and identified and reviewed hundreds of peer-reviewed scientific journal articles. In addition, clone producers provided data from independently analyzed blood samples of clones that we then evaluated along with the health records for those animals, and compared against the equivalent data from conventionally bred animals of the same age, breed, and raised on the same farms. All of the data evaluated in the Risk Assessment are either available in peer-reviewed publications, or in the Risk Assessment itself. In addition, the methodology used to evaluate the data, underlying assumptions used by the risk assessors, residual uncertainties, including sources of potential bias and the basis for our conclusions are explicitly provided in the Risk Assessment.

After several years of analysis, FDA's CVM scientists and veterinarians found that health risks do not appear to be increased in clones that survive beyond a few weeks of birth, and that a healthy adult clone could not be distinguished from a healthy conventionally bred animal. Blood values, enzymes, overall health, and behavioral observations for those clones are all in same ranges seen in conventionally bred animals of the same breed and raised on the same farms. In addition, meat and milk from clones do not appear to differ significantly in composition from meat and milk from conventionally bred animals.

SUMMARY OF THE RISK ASSESSMENT (RA) FINDINGS:

Source of Hazards

The Risk Assessment specifically excludes genetically engineered animals. No new genes have been introduced into these clones, and all of the genes present in clones come from their traditionally bred domestic livestock counterparts. Because of their long history of safe use as food, domestic livestock are not thought to produce toxic substances. Therefore, hazards to and from clones themselves would result from epigenetic dysregulation (the inappropriate expression of genes, including over- or under-expression, or expression at the wrong time). Hazards arise similarly in animals generated via other ARTs. The goal of this Risk Assessment has been to determine whether any unique hazards arise that are not noted in comparators, or that have not been identified in cattle, swine, sheep, or goats produced via other ARTs. FDA thus developed the Comprehensive Biological Systems Approach (CBSA), which systematically evaluates all the available data on animals involved in cloning (clones and their surrogate dams) on a developmental stage basis.

Food Consumption Conclusions

Clones: As a baseline, clones and food products derived from them would be subject to all of the same federal, state, and local regulations as conventional livestock. By using the CBSA, and analyzing physiological, anatomical, health, and when available, behavioral data, we have determined that anomalies present in cattle, swine or goat clones are the same as those associated with any other ART. In fact, these animals meet all of the developmental milestones appropriate for their species, and become otherwise indistinguishable from sexually-reproduced comparators. In addition, we evaluated the available information on the composition of milk from bovine clones, and did not find any significant differences between milk from clones and milk from sexually-reproduced cows. We therefore conclude that food products derived from cattle, swine, and goat clones pose no more risk than food derived from sexually reproduced animals. Insufficient information was available to make a decision on food consumption risks from clones of species other than cattle, swine, and goats.

The Risk Assessment clearly states that different degrees of uncertainty accompany our conclusions for each species, and identifies the sources of those uncertainties. Therefore, the food consumption-related measures in the Risk Management Plan that follows are, in large part, managing uncertainties.

Progeny: For clone progeny (i.e., sexually-reproduced offspring of clones), we agree with the National Academies of Science (2002) that there is no anticipated additional risk of epigenetic dysregulation compared to animals of conventional breeding lineages. In fact, known aberrant phenotypes caused by epigenetic dysregulation in mouse clones have not been shown to be heritable. We therefore conclude in the Risk Assessment that food from any progeny of a clone poses no more risk than food from any other sexually-reproduced animal.

Food Safety Uncertainties

Uncertainties arise from three categories of information: our use of available empirical data, our use of biological assumptions, and perhaps most importantly, changes in the technology used to produce clones.

1. Empirical data. In general, the degree of confidence that can be placed in conclusions arising from large data sets is higher than from smaller or incomplete data sets. Because the most extensive data sets that we reviewed were submitted by an individual laboratory or producer, the uncertainties associated with the conclusions drawn from them are lower than for smaller data sets. We have adjusted for small studies and incomplete data sets reported in the peer-reviewed literature by developing and using the CBSA approach, which allowed us to evaluate all of the data, regardless of its source, across developmental nodes to determine whether common anomalies could be detected. Since the release of the Draft Risk Assessment, we have continued to monitor the literature and have updated this final version of the Risk Assessment with relevant publications and additional unpublished data that have been submitted to us.

2. Biological assumptions. The scientific community's understanding of the epigenetic processes involved in early embryonic development is still imperfect, however, knowledge about the molecular mechanisms involved is growing. There currently appears to be general agreement that epigenetic dysregulation is responsible for the anomalies observed in clones. The exact mechanism(s) by which dysregulation occurs (or correct regulation persists) is not yet well understood. Because of this biological uncertainty, we will carefully monitor this expanding field to ensure that the positions commonly held on epigenetic mechanisms, especially as they apply to clones, will continue to be supported. Our monitoring will consist of surveying the literature, maintaining our attendance at such scientific and professional meetings that address epigenetic reprogramming, including the International Embryo Transfer Society, and others as appropriate.

3. Technology Changes. Even though the Risk Assessment evaluates clones themselves rather than the methods used to produce clones, in fact, most of the clones considered in the Risk Assessment were developed using relatively similar methods. Major changes in the technology used to produce clones may introduce uncertainty, as might application of the technology to produce clones of food-producing species not considered in the Risk Assessment.

Given the rapid pace of advances in this technology, it is very likely that new cloning methods are currently being developed and will be implemented in the future. Because uncertainties may arise due to the changing techniques or new species being cloned, we plan to continue to monitor the technology, and the science underlying it, so that we can determine whether new developments introduce hazards not observed with the present cloning methods.

Animal Health Risks

Animal health risks are defined as the adverse health outcomes observed in clones and their surrogate dams. No adverse health outcomes were observed in clones (or their surrogate dams) that have not also been observed with other ARTs currently used in modern agricultural practices. The frequency of the adverse outcomes is, however, increased.

Surrogate dams bearing cattle and sheep clones show an increased frequency of adverse outcomes compared to dams bearing non-clone pregnancies. This increase is not seen in swine and goat surrogate dams bearing clone pregnancies. Early reports of cloning in cattle and sheep indicated that most clone pregnancies failed to result in live births. As the technology improves, however, the proportion of live, normal births appears to be increasing. Most of the increased risk for cattle and sheep clones appears to be related to large offspring syndrome (LOS), although other developmental defects are observed.

As clones of every species evaluated grow and develop, they appear to become as healthy as their conventional counterparts. No health risks appear to be increased in apparently normal clones that survive beyond a few weeks of birth. Cattle clones in the 6-18 month cohort are virtually indistinguishable from their age- and breed-matched comparators.

OTHER CONCERNS: We recognize that animal cloning raises many issues in addition to animal health and food safety. Moral, religious, and ethical concerns about animal cloning for agricultural purposes have been raised in several fora, including in comments during the November 2003 Veterinary Medicine Advisory Committee meeting presenting the preliminary findings of the Risk Assessment (see http://www.fda.gov/cvm/CVM_Updates/03VMACTrans.htm), as well as public comments submitted to the agency on the Draft Risk Assessment and the Proposed Risk Management Plan. We also recognize that these other issues may become intertwined with health and safety issues. Although it is not within the agency's charge to address these types of ethical issues regarding animal cloning, we are willing to participate in such discussions as they continue to be held in various fora to provide our scientific expertise. We note, however, that the Risk Assessment is strictly a science-based evaluation of animal health and food consumption risks, and the Risk Management Plan and Guidance for Industry do not address any ethical or other non-science based concerns regarding animal cloning for agricultural purposes that are unrelated to FDA's public health mission.

RISK MANAGEMENT PLAN**:** We developed this Risk Management Plan with the following principles in mind:

- The basis for the management proposals should be derived from the science underpinning the identified risks or uncertainties;
- Risk management should be commensurate with the magnitude and severity of identified risks; and
- Implementation of the risk management proposal should be straightforward and unambiguous.

Risks from Food and Feed Derived from Clones

Feed:

No feed risks unique to clones were identified. Therefore, as stated in our accompanying 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.

Food:

The results of the Risk Assessment have clearly indicated that cloning falls on the continuum of assisted reproductive technologies (ARTs), that no anomalies have been observed in animals produced by cloning that are not also observed in animals produced by other ARTs and natural mating. The Risk Assessment has also determined that there is sufficient information to determine that food from cattle, swine, and goat clones is as safe to eat as that from their more conventionally-bred counterparts. We therefore do not believe that meat or milk from cattle, swine, and goat clones would require any additional controls compared with meat or milk from cattle, swine, or goats currently entering the food supply today (e.g., ante- and post-mortem inspections or the Pasteurized Milk Ordinance, and/or other federal, state, or local requirements, as appropriate).

Risks from Food Derived from Clone Progeny

No food consumption risks were identified for clone progeny. Therefore, in our Guidance for Industry, we state that food products from the sexually-reproduced *offspring of clones are suitable to enter the food and feed supply under the same controls as applied to any animal that is the product of sexual reproduction*. We anticipate that most of the food products from this technology will be derived from clone progeny.

Surveillance for Changes in Cloning Technology and State of Knowledge that Could Affect Food Safety

The risk management measure for any residual uncertainties about the safety of food and feed derived from clones and their progeny includes FDA's *continuing surveillance of the state of*

the science through continued consultations with clone producers, monitoring the scientific literature, and participating in scientific and professional society meetings, and discussions with clone producers. We anticipate that this surveillance will continue indefinitely as part of the agency's ongoing efforts to maintain currency with key issues regarding animal health and food safety.

Animal cloning technologies are relatively new and steadily evolving. The Risk Assessment has compiled the most extensive review to date of the publicly available animal health and food composition data on animal clones and their progeny. As with any new technology involved in the production of food, FDA will actively monitor the state of the science for changes in the technology that may introduce new concerns not currently identified, or modify existing concerns. Should the agency identify any issues that would likely have an impact on food safety, we will take appropriate action, including consulting with the United States Department of Agriculture's Food Safety and Inspection Service. In particular, we will

1. *Monitor and review additional animal health and food composition data on animal clones or their progeny as they become available.*

    - FDA will establish a close liaison with professional and scientific organizations such as the International Embryo Transfer Society (IETS), the Federation of Animal Science Societies, and the American Veterinary Medical Association to collect and access new animal health and production data as they become available, and will work with these organizations to collect and maintain an international, centrally-located database of animal clone and progeny health and production data, which would be made publicly available. In particular, the FDA is currently engaged in an ongoing project with the IETS to produce a publicly available international data base on the health of clones and the composition of food from them. This data base should become available in 2008.

2. *Monitor and review changes in animal cloning techniques and technologies.*

    - FDA will routinely monitor the scientific literature and attend pertinent scientific conferences to stay abreast of animal cloning technologies. FDA will continue to maintain open and informal channels of communication with animal clone producers and researchers to remain up-to-date with these technologies.

3. *Continue to consult with clone producers to review changes in the technology.*

    - FDA will continue to consult with clone producers to review changes in the technology. Clone producers with questions regarding whether their technology is different from that evaluated in the Risk Assessment are strongly encouraged to discuss their technology with FDA.

4. *Monitor and maintain knowledge base on the biology of epigenetic mechanisms governing gene expression and their role in nuclear transfer.*

- FDA will maintain an ongoing awareness of the scientific literature regarding the biology of animal clones and epigenetics, maintaining our scientific currency in accordance with our regulatory mission.

Risk to the health of animals involved in cloning

Increased risks of adverse health outcomes of the types previously observed in animals produced via other ARTs have been observed in surrogate dams and very young clones. Animal cloning, particularly in cattle and sheep, is associated with an increased risk of adverse health outcomes in the surrogate dams carrying late-term clone fetuses, as well as very young clones. Specific health issues of concern for the surrogate dams include the increased incidence of prenatal hydroallantois and/or hydrops in the surrogate dams carrying clone pregnancies to term. Health issues of concern for the clones themselves include perinatal symptoms related to LOS including, but not limited to, pulmonary and/or renal insufficiency, difficulty maintaining body temperature, and umbilical hernias.

In order to minimize the impact(s) of these animal health risks, we have been working with the International Embryo Transfer Society to prepare a publicly available manual on animal care standards for animals involved in the cloning process. This document is due to be released to the public on IETS' website in early 2008.

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