Animal Cloning:

Proposed Risk Management Plan for Clones and their Progeny

December 28, 2006

ADDRESSES:

1. Single copies of this Proposed 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 Proposed Risk Management Plan is also available on the Internet at: http://www.fda.gov/cvm/cloning.htm.

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 The accompanying Draft Risk Assessment and Draft Guidance for Industry are also available from the above address and internet site.

3. Send written comments on this Proposed Risk Management Plan to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, room 1061, Rockville, MD 20852. Submit electronic comments to: http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm?AGENCY=FDA. Written comments should be identified with the docket number found in the heading of this document. For convenience in reviewing the comments, FDA requests that comments be separately identified as to whether they apply to the Draft Risk Assessment, the Proposed Risk Management Plan, or Draft Guidance for Industry. All comments received will be considered part of the public record and will be available for viewing on the Internet at http://www.fda.gov/ohrms/dockets/ and in the FDA docket room between 9:00 a.m. and 4:00 p.m. Monday through Friday.

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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 Proposed Risk Management Plan is designed to identify the relevant issues to be considered in managing risks associated with animal cloning and to present proposed 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 Draft 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 are beyond the purview of the agency. Therefore, although FDA acknowledges that all relevant issues need to be considered, some of these issues cannot be addressed within the scope of this proposed 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 Draft 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 Draft 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 DRAFT RISK ASSESSMENT. The Draft 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 Draft Risk Assessment is on those domestic livestock that have been cloned, i.e., cattle, swine, sheep, and goats.

In the Draft 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 Draft Risk Assessment are either available in peer-reviewed publications, or in the Draft 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 Draft Risk Assessment.

After four years of analysis, FDA's CVM scientists and veterinarians found that they could not distinguish a healthy adult clone 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, based on the available data, meat and milk from clones do not appear to differ significantly in composition from meat and milk from conventional animals.

SUMMARY OF THE DRAFT RISK ASSESSMENT (RA) FINDINGS:

Source of Hazards

The Draft Risk Assessment specifically excludes genetically engineered animals; all of the genes present in the nuclei of the cells of the resulting clone come from the donor animal. 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 Draft 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 there are no anomalies present in cattle, swine or goat clones that are different from 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 that pass government food safety inspections pose no more risk than food derived from sexually reproduced animals. Insufficient information was available on sheep clones to make a decision on food consumption risks.

The Draft 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 Proposed 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 Academy of Sciences (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 Draft 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.

We are aware that additional studies on the health of clones and the composition of edible products derived from them are underway by various organizations in the U.S. and abroad. Our preliminary review of the information that we have seen suggests it is consistent with our conclusions in the Draft Risk Assessment regarding animal health and food safety. We will review any new data that become available and other relevant information submitted during the public comment period and make any necessary revisions to the final Risk Assessment.

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.

3. Technology Changes. Even though the Draft Risk Assessment evaluates clones themselves rather than the methods used to produce clones, in fact, most of the clones considered in the Draft 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 Draft 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. Concerns about the ethics of animal cloning have been raised in several fora, including in comments during the November 2003 Veterinary Medicine Advisory Committee meeting presenting the preliminary findings of the Draft Risk Assessment (see http://www.fda.gov/cvm/CVM_Updates/03VMACTrans.htm). We also recognize that these other issues may become intertwined with health and safety issues. Although it is not within the agency's purview to address any 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 Draft Risk Assessment is strictly a science-based evaluation of animal health and food consumption risks, and the Proposed Risk Management Plan and Draft Guidance for Industry do not address any ethical or other non-science based concerns regarding animal cloning.

PROPOSED RISK MANAGEMENT PLAN**:** We developed this Proposed 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 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.

Food:

Various systems are in place in the United States to assure the safety of human food. These food safety systems do not currently require that information be provided on the method by which the animals were produced, e.g., natural mating, assisted reproductive technologies, etc. No anomalies have been observed in animals produced by cloning that are not also observed in animals produced by other assisted reproductive technologies (ARTs) and natural mating. Accordingly, food from animal clones would be subject to the same food safety systems as food from any other animal. Therefore, animal clones that pass ante- and post-mortem inspection would be considered as safe as any other animals that pass those inspections. Similarly, milk from animal clones that is subject to the PMO and/or other federal, state, or local requirements and meets those requirements would be considered as safe as any other milk which is subject to and meets those requirements.

Risks from Food Derived from Clone Progeny

No food consumption risks were identified for clone progeny. Therefore, in our Draft 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.

Animal cloning technologies are relatively new and steadily evolving. The Draft 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. 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 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.

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 Draft 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 have been observed in surrogate dams and very young clones. Working with professional societies dedicated to animal health and the care of food-producing animals, such as those associated with veterinary medicine or the practice of embryo transfer, FDA will encourage the *development of standards of care for animals involved in the cloning process* (i.e., clones and their surrogate dams).

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 propose to work with professional and scientific organizations whose missions include ensuring the health of animals to establish animal health assessment and care standards for surrogate dams and clones.

We would look to partner with organizations having expertise in cloning technologies, and to establish direct liaisons with academic and industry scientists for their recognized international expertise in animal health and safety management. In addition, we will partner with the veterinary community regarding animal evaluation and care issues.

REFERENCES:

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Ron Gillespie. 2002. Marketing Clones. Who’s Buying? In: Animal Cloning and the Production of Food Products: Perspectives From the Food Chain, Proceedings from a workshop sponsored by the Pew Initiative on Food and Biotechnology and the Center for Veterinary Medicine of the U.S. Food and Drug Administration. September 26.
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