Preface

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The following Risk Assessment is the result of a multi-year effort by staff from the US Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM or the Center). Since the late 1990s, CVM has been gathering data and meeting with clone producers and other stakeholders interested in cloning to discuss the safety and regulatory implications of somatic cell nuclear transfer (SCNT), the process most commonly used to generate animal clones during this time period. In the fall of 2000, CVM tasked the National Academy of Sciences (NAS) to perform an independent, scientific review of the available data on the safety of cloning, including holding a public meeting to identify science-based concerns and elicit data and information on clones and their food products from the scientific community. In July of 2001, the Center issued a CVM Update requesting that clone producers not introduce meat or milk from clones or their progeny into food or feed until the NAS report had been completed, and the agency had had a chance to complete its own review of the safety of those food products.[1]

In October of 2002, NAS issued its report "*Animal Biotechnology: Science-Based Concerns*." Following an overview of the available data on animal clones, the report indicated that the most likely mechanism for generating hazards to clones would stem from reprogramming of the donor cell genome, and that any harms that might result from that reprogramming would be observed early in a clone's development. They further noted that there were no published data comparing the composition of meat or milk from clones with that from conventionally-bred animals. Nonetheless, the report concluded that there is "no evidence that food products derived from adult somatic cell clones or their progeny pose a hazard (i.e., there is no evidence that they present a food safety concern)" (page 65).

This Risk Assessment is CVM's subsequent independent analysis of all of the available data relevant to assessing the health of clones and their progeny (and other animals involved in the cloning process) or food consumption risks resulting from edible products from these animals. In order to make the Risk Assessment as transparent as possible, all of this information is available to the public, either by virtue of its publication in peer-reviewed journals, or by "publication" in this risk assessment. We have actively sought independent peer-review of these data by providing all of the data in raw form (not summaries) either in the text of the risk assessment or in appendices. In addition, we have also described the means by which the methodology was developed to facilitate peer-review by risk assessors.

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[1] http://www.fda.gov/cvm/CVM_Updates/clones.htm

CVM has attempted to be as comprehensive as possible about identifying and using all of the relevant data in its analysis. We have performed extensive literature reviews, engaged in conversations with scientists involved in cloning animals, and requested data on animal health and food composition from scientists, breeders, and food producers. Unpublished data were provided to us in raw, unanalyzed form, which we subsequently analyzed. CVM determined whether a particular publication or dataset was relevant to the analysis. These judgments were framed by the two overarching objectives of the Risk Assessment: determining whether cloning poses any health risks to the animals involved in the cloning process, and whether any hazards arise during the development of clones or their progeny that may pose food consumption risks.

Literature searches for the draft version of the Draft Risk Assessment ceased in early 2006. For the final version of the Risk Assessment, we have conducted updated literature searches (through mid-year 2007), thoroughly reviewed hundreds of additional relevant papers from the peer-reviewed literature, and incorporated this information into the Risk Assessment. The final version also includes additional, unpublished data that were submitted to CVM after the release of the Draft Risk Assessment. We reviewed all of the public comments that we received on the Draft Risk Assessment and associated documents. Careful consideration was given to relevant, science-based information in the comments, and parts of the Risk Assessment have been revised in response to these comments.

In addition to understanding the Risk Assessment's goals, it is equally important to understand what it does not consider. It does not attempt to address the question of whether clones are "normal;" rather it concentrates on identifying the risks that cloning poses to animal health or to humans and animals consuming food derived from clones and their progeny. It also does not attempt to explore issues such as the influence of different donor cell types or cell cycle stages in the "success rate" for producing clones, or the degree to which clones are more or less identical at the phenotypic level. Studies addressing these questions have been used, however, when they provided data useful to the identification of hazards or risks. Similarly, the Risk Assessment does not attempt to parse out the relative effectiveness of different cloning techniques or different laboratories in generating live animals. Results of cloning in species not commonly used for food have been employed only as they have utility as model systems (*e.g.*, mice as models for livestock). Uncertainties associated with those models have been identified.

It is important to note that this Risk Assessment is a scientific document that provides a framework by which science-based questions regarding animal health and food consumption risks are evaluated. CVM recognizes that cloning raises many ethical and

economic concerns. These issues may be important to members of the public, however, they are not within FDA's mission and therefore not within the purview of this Risk Assessment.

Finally, the measures we will take to manage the risks associated with cloning and our recommendations regarding the use of clones or their progeny as food or feed are not included in the Risk Assessment, but are addressed in the accompanying Risk Management Plan and Guidance for Industry.

Chapter I:

Executive Summary

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Cloning is the colloquial term used to describe the process of somatic cell nuclear transfer (SCNT) that falls on a continuum of assisted reproductive technologies (ARTs) currently used in agriculture. In this Risk Assessment, the Center for Veterinary Medicine (CVM or the Center) at the US Food and Drug Administration (FDA) presents a science-based review of the available information on cloning in species traditionally used for food (*i.e.*, cattle, swine, sheep, and goats).

A. Overview

This Risk Assessment addresses SCNT technology, its impact on the health of animals involved in that process, and food consumption hazards that may arise in animal clones and their progeny[2] in the context of the use of ARTs in conventional animal agriculture. Chapter II is a summary of ARTs currently used in food animal breeding and a detailed explanation of SCNT. Chapter III describes the process of risk assessment, its application to animal cloning, and the nature of the hazards that may arise as the result of cloning. A synopsis of the processes involved in epigenetic reprogramming and their relevance to adverse outcomes noted in animals derived via SCNT and other ARTs is found in Chapter IV. Chapter V addresses potential health risks to animals involved in the process of cloning, including surrogate dams, clones, and their progeny. Chapter VI addresses potential food consumption risks that may result from edible products derived from animal clones or their progeny. Each chapter contains conclusions relevant to that subject; the Risk Assessment is summarized in Chapter VII, and our overall conclusions are presented there. In order to make this process as transparent as possible, all of our methodologies are presented in the text of the risk assessment; the information and data that CVM evaluated are publicly available, either in peer-reviewed publications, or in Appendices to this document. The process by which CVM drew its conclusions is presented in the Risk Assessment, along with explicit statements of potential bias and uncertainty. The document concludes with a complete bibliography, a glossary of terms, and appendices containing data and background information.

The Risk Assessment is the result of a qualitative analysis that identifies and characterizes the nature of hazards that may be introduced into animals as a result of cloning, and puts them in the context of other ARTs currently practiced in the United States. The strongest conclusions that

[2] For the purposes of this analysis, a clone is defined as an animal produced asexually from a single animal by somatic cell nuclear transfer. Clones are thus genetically identical to their nuclear donor animal. Progeny of clones have at least one animal clone as a parent (but could also result from mating two animal clones) and are produced by sexual reproduction. Clones of clones would be considered as clones (*i.e.*, directly arising from an SCNT process).

can be drawn regarding positive outcomes in risk assessments of this type are "no additional risk" because outcomes are weighed against known comparators. If a finding of "no additional risk" were to be applied to the health of animal clones, it would mean that the cloning process would not pose any greater risk to the health of the animals involved than other ARTs. Applied to the safety of edible products derived from clones, a finding of "no additional risk" would mean that food products derived from animal clones or their progeny would not pose any additional risk relative to corresponding products from conventional animals, or that they are as safe as foods that we eat every day. As with all risk assessments, some uncertainty is inherent either in the approach we have used or in the data themselves. Where uncertainties exist, CVM has attempted to identify the degree of uncertainty and the reasons for its existence.

B. Technology Overview (Chapter II)

Assisted reproductive technologies (ARTs) have been employed extensively in animal agriculture for over a century, and at least one (artificial insemination) has been practiced for several hundred years. These technologies form a continuum that ranges from the fairly minimal assistance provided to animals engaged in natural service through the more recent development of SCNT. ARTs have aided in the genetic improvement of domestic livestock species by the selection and propagation of desirable phenotypes, and accelerating the rate at which those characteristics have been incorporated into national herds. Artificial insemination, for example, permitted the propagation of valuable genomes without the sire being physically present, thereby allowing superior genetics to be spread beyond relatively small geographical areas.

Most commonly used ARTs rely on fertilization as a first step. This joining of egg and sperm is accompanied by the recombination of the genetic material from the sire and dam, and is often referred to as "shuffling the genetic deck." From a breeder's perspective, phenotypes resulting from sexual reproduction cannot be predicted—that is, the characteristics of the offspring from a mating may be estimated, but not predicted with certainty. Nuclear transfer, the most advanced of these technologies, does not require fertilization and allows for the propagation of known genotypes and phenotypes without the risk of genetic reshuffling. Thus, SCNT's greatest immediate impact on animal agriculture may be that it allows the propagation of genomes whose phenotypes are proven. It also allows the propagation of animals whose reproductive function may be impaired, or of very valuable animals that have died. 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.

C. Risk Assessment Methodology (Chapter III)

Risk assessment is a science-based process used to identify hazards that may be present in predefined exposure scenarios, and to estimate the severity and chances of the outcome(s) occurring once that exposure occurs. Because many, if not all, of the individual steps that comprise a risk assessment contain various degrees of uncertainty, risk assessors should explicitly describe the sources of uncertainty and the effect(s) that the uncertainties may have on any judgment of risk. Risk assessment serves as the scientific underpinning from which risk managers may choose different options based on their understanding of, and responsibilities to, the broader contexts within which they operate.

Qualitatively, risk may be thought of as some function of the combination of exposure and the intrinsic properties of the substance or process under consideration by linking an exposure to the likelihood of an outcome. When performing a risk analysis, it is critically important to distinguish between a *hazard* and the potential *risk(s)* that may result from exposure. A *hazard* can be defined as an act or phenomenon that has the potential to produce an adverse outcome, injury, or some sort of loss or detriment. These are sometimes referred to as *harms*, and are often identified under laboratory conditions designed to maximize the opportunity to detect adverse outcomes. Thus, such observational summaries are often referred to as "*hazard identification*" or "*hazard characterization.*" Risk, then, is the conditional probability that estimates the probability of harm given that exposure has occurred. In a qualitative assessment such as this, however, risks can be discussed only within a qualitative context, and no quantitative interpretations should be made.

In order to address the hazards and risks to animals involved in cloning and the food products derived from them four issues must be addressed: identifying hazards and risks; determining the degree to which existing data address the question of risk; characterizing residual uncertainties; and selecting the most appropriate definition of risk for the risk assessment.

This Risk Assessment explicitly excludes transgenic clones from the identification of hazards or risks experienced by "just clones" because of the inability to determine whether the transgenic event or cloning was causally associated with an adverse outcome. In addition, the Risk Assessment has assumed that, at minimum, animal clones, their progeny, and food products derived from them would be subject to the same laws and regulations as conventional animals and their food products.

Source of Hazards/Risks: Because no exogenous genes have been introduced into animals derived via SCNT, the underlying assumption regarding potential hazards that could arise is that anomalies observed in animal clones are due to incomplete or inappropriate reprogramming of

the donor cell nucleus. These anomalies may be macroscopic (*e.g.*, anatomical abnormalities, difference in size or growth rate, reduced fertility, morbidity, mortality) or they may be more subtle in nature. Potential *subtle hazards* would allow an animal clone to develop with apparently normal appearance and functions, but with sub-clinical physiological changes.[3] These include alterations in clinical chemistry, hematology, or changes in physiological set-points (*e.g.*, changes in hormone levels). For food consumption risks, relevant subtle hazards that might result from inappropriate or incomplete reprogramming include alterations in the expression of key proteins affecting the nutritional content of food, possibly leading to dietary imbalances. Similar hazards arise in animals generated via other ARTs or natural breeding. The goal of this risk assessment is to determine whether any unique hazards arise that are not noted in comparators, or have not been identified in cattle, swine, sheep, or goats produced via other ARTs or natural breeding.

To address animal health and food consumption risks associated with cloning, two complementary approaches were employed. First, information on the health of animal clones was evaluated within a framework developed by CVM called the *Critical Biological Systems Approach* (CBSA). For food consumption risks, the CBSA was applied in combination with a second approach referred to as *Compositional Analysis*. Following review of all of the available data using the CBSA and Compositional Analysis, a *weight of evidence approach* was then used to draw conclusions regarding risks to animals associated with cloning, and risks to humans from consuming foods produced by animal clones.

The CBSA: This approach divides the life cycle of an animal clone into five functional developmental nodes. Developmental Node 1 incorporates the initial technical steps involved in SCNT (cell fusion) and continues through fetal development. Developmental Node 2 encompasses the perinatal period, including labor induction in the dam, delivery, and the critical few days after birth. The third developmental node, Juvenile Development and Function, covers the period of rapid growth between birth and the onset of puberty. The Reproductive Development and Function Node (Developmental Node 4) includes puberty and reproductive function throughout the reproductive life of clones. The Post-Pubertal Maturation Node (Developmental Node 5) consists of all non-reproductive functions of sexually maturing or mature clones, including growth, weight gain, disease frequency, aging, and, where available, lifespan.

The nature of each component of the risk assessment (*i.e.*, animal health or food consumption risks) shaped the manner in which the available data were evaluated using the CBSA. For example, identification of adverse outcomes for animal health included both the animal clone

[3] Such subtle hazards are not typically included in standard food safety assessments.