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Division of Dockets Management (HFA-301)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Risk Assessment and Risk Management Plan for Clones and Their Progeny  
Docket No. 2003N-0573

The Union of Concerned Scientists (UCS) is pleased to submit the following comments on the Draft Risk Assessment and Proposed Risk Management Plan for Clones and Their Progeny published by the Center for Veterinary Medicine on December 28, 2006.

UCS is the leading science-based non-profit working for a healthy environment and a safer world. UCS combines independent scientific research and citizen action to develop innovative, practical solutions and secure responsible changes in government policy, corporate practices, and consumer choices. UCS's Food and Environment Program seeks to transform the U.S. food system into a sustainable enterprise.

## **I. BACKGROUND**

Cloning technology encompasses techniques capable of producing nearly identical genetic copies<sup>1</sup> of animals born at different times. The seminal cloning technology, referred to as somatic cell nuclear transfer (SCNT), is a multi-step procedure entailing the insertion of a nucleus into an enucleated egg, the initiation of development, and the implantation of the egg into a surrogate dam where it completes gestation.

Animal scientists have long been able to produce genetic copies of animals, usually by separating embryonic cells early in development (embryo splitting) or performing nuclear transfers from embryonic cells (blastomere nuclear transfer). These techniques produce relatively small numbers of copies all born at the same time. SCNT opens up the possibility of very large numbers of genetic copies born long after the birth of a progenitor organism.

The announcement of Dolly the sheep, the first SCNT clone to survive to adulthood, gave rise to a storm of publicity and debate. The controversy revolved primarily around human cloning and issues like biological determinism, individuality, and the redefinition of the family, but also considered issues of food safety and animal welfare. The public debate easily moved beyond Dolly to humans because of the wide recognition that animal cloning is an essential stepping stone to cloning human beings.

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<sup>1</sup> Clones differ genetically from their progenitors in a number of ways. One way is that the mitochondrial DNA in the cytoplasm of the egg comes from the egg donor rather than the progenitor.

## **A. The National Research Council Report**

The task of responding to the issues raised by animal cloning has fallen primarily to the Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM).

In 2001, FDA ("the Agency") imposed a voluntary moratorium on the sale of the products of cloned animals and their progeny into the human and animal food supplies and began assessing the risks expected from the cloning of food animals. In 2001, the CVM approached the National Research Council (NRC) of the National Academies and requested that it convene an expert committee to look at the animal health, food safety, and environmental risks associated with new products of animal cloning among other new animal biotechnologies.

In 2002, the NRC produced a report called *Animal Biotechnology: Science-Based Concerns*<sup>2</sup> focused on risks associated with new animal biotechnologies, primarily cloning and genetic engineering. On the consumption of foods from cloned animals, the report concluded that "there is no current evidence that food products derived from adult somatic cell clones or their progeny present a food safety concern," but it would be "difficult to identify concerns without additional supporting data."<sup>3</sup>

On the animal health and welfare issues, the committee found the issues difficult to assess, but considered the potential of technologies to cause pain, distress (both physical and psychological), behavioral abnormalities, physiological abnormalities, and/or health problems.<sup>4</sup>

But the report went beyond the science-based concerns the NRC was asked to discuss, and considered broader policy and institutional concerns. The committee pointed out that "socially, politically, and ethically determined factors influence both the nature of scientific research and the interpretation of data," noting that the introduction of new technologies is often intertwined with ethical, socioeconomic and cultural issues.<sup>5</sup>

The NRC report acknowledged that the ethical, social and cultural concerns were not the mission of risk-based agencies and would be unlikely to be examined comprehensively by such agencies.<sup>6</sup> The committee did not list settings where such concerns would be considered, but did include its own brief discussion of ethical and social issues in the report.<sup>7</sup>

## **B. The FDA's First Risk Assessment on Cloned Animals**

In October 2003, the FDA released its first risk assessment based on studies culled from the scientific literature and from companies involved in the cloning business, concluding that cloned animals were safe to consume.<sup>8</sup> A week after its publication, the risk assessment was roundly

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<sup>2</sup> National Research Council of the National Academies, *Animal Biotechnology: Science-based Concerns*. 2002. The National Academies Press, Washington, DC. (Hereinafter "NRC Report")

<sup>3</sup> NRC Report at 9.

<sup>4</sup> NRC Report at 11.

<sup>5</sup> NRC Report at 13.

<sup>6</sup> NRC Report at 120.

<sup>7</sup> NRC Report at 116-121.

<sup>8</sup> Weise, E. Cloned Food Gets Closer to Market. *USA Today*, October 30, 2003.

rejected by the FDA's Veterinary Medicine Advisory Committee (VMAC), which found that the FDA's CVM had not provided enough data to support that conclusion of safety, and asked for more studies.<sup>9</sup>

### **C. The Current Risk Assessment**

The current set of documents released by the FDA includes a risk assessment, a risk management plan, peer reviews of the agency's analysis, frequently asked questions, and raw data from selected studies. Below are brief descriptions of relevant parts of those documents.

#### 1. The Risk Assessment

The FDA risk assessment looks at cloned cattle, pigs, goats, and sheep and is limited to two risk issues—safety for human consumption, and animal health. Like the earlier risk assessment, this one is based almost exclusively on studies found in the published literature, supplemented by a few studies done by two companies currently in the animal cloning business and provided voluntarily to FDA.

Unfortunately, although the literature on cloning may seem voluminous, it contains very few studies specially designed to answer the questions at the heart of the FDA's risk assessment: food safety and animal health. A small core of studies—only some of which are peer-reviewed—is used over and over in the assessment. For example, most of studies considered in the chapter devoted to food consumption risk (Chapter VI) are basically studies on the cloning process or animal health rather than food safety. They look at a variety of topics, such as growth rates, methods of cloning, and behavioral variability, which have only a remote relationship to food safety risks. And, in fact, Chapters IV and V heavily rely on the same studies. FDA included the studies in an effort to find clues that might suggest food safety concerns<sup>10</sup> and we applaud that effort. But all that analysis can obscure the lack of a strong set of peer-reviewed studies directly addressed to the topics at issue. As we discuss below, FDA is forced to rely on tangential studies because it does not have the authority to compel the kinds of studies it needs.

Because there are relatively few relevant studies in the scientific literature, the Agency developed a systematic and transparent approach to assessing risk that combines numerous assumptions and the few available studies into what it terms a “weight of the evidence” approach to support its conclusions.

#### 2. Major Conclusions

The major conclusions of the risk assessment are as follows:

*On food consumption risks.* “The products from normal, healthy clones or their progeny do not appear to pose increased food consumption risks relative to comparable products from conventional animals.”

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<sup>9</sup> Olson, E. Panel Doubts Finding That Cloned Food is Safe. *The New York Times*, November 5, 2003.

<sup>10</sup> FDA Risk Assessment: Food Consumption Risks, Chapter VI at 1. (Hereinafter “Food Consumption Risks”)

“Confidence in this conclusion is relatively high due to empirical evidence from bovine clones, and the consistency of empirical observations among other species.”<sup>11</sup>

“The uncertainties associated with this judgment are a function of the empirical observations and underlying biological process contributing to the production of clones.”

Since there were virtually no data on sheep other than Dolly, the Agency decided not to allow the products of cloned sheep on the market.

*On animal health.* “SCNT can pose an increased frequency of health risks to animals involved in the cloning process, but these do not differ qualitatively from those observed in other ARTs [assisted reproductive technologies] or natural breeding. The frequency of live normal births appears to be low, although the situation appears to be improving as the technology matures.”<sup>12</sup>

*On the food consumption risks associated with the sexual progeny of clones.* “Nevertheless [despite complete absence of data], we do not believe that consumption of edible products from clone progeny would pose any additional risk relative to the consumption of similar products from non-clone progeny.”<sup>13</sup>

### 3. Comparative Standards

The FDA expressed the conclusions of its risk assessment on both food safety and animal health not in simple straightforward terms, but as compared with other animals used as food.

Thus, milk and meat from clones are not deemed safe, but rather appear to pose “no increased food consumption risk(s) relative to comparable products from sexually-derived animals”.<sup>14</sup> And the high failure rate of animal cloning was deemed acceptable not standing alone but because the risks do not “differ *qualitatively* from those observed in other ARTs or natural breeding.”<sup>15</sup> (emphasis ours)

## **D. The Current Risk Management Plan**

### Food Consumption Risks

On the basis of its conclusions on food safety, FDA proposes no special oversight of the technology. Under the risk assessment, animal producers will have carte blanche to produce and sell clones and their products for food. The Agency does not propose any further testing or any formal monitoring of animal clones or their progeny.

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<sup>11</sup> Animal Cloning: A Risk Assessment, Executive Summary.

<sup>12</sup> Animal Cloning: A Risk Assessment, Chapter VII, Summary and Conclusions, at 3.

<sup>13</sup> Animal Cloning: A Risk Assessment, Executive Summary at 11.

<sup>14</sup> Animal Cloning: A Risk Assessment, Chapter VII, Summary and Conclusions at 3.

<sup>15</sup> Ibid.

## Animal Health

On the basis of its findings that animal health is within the scope of ARTs, the Agency proposes no restrictions on further experiments with clones.

### **E. Labeling**

The FDA is not recommending labeling of the products of clones or their progeny because in its view there is no science-based reason to use labels to distinguish products derived from clones from the products of conventional animals.<sup>16</sup>

### **F. Legal Authority**

The Risk Assessment and Risk Management documents issued by FDA are not embedded in a policy or legal framework. The documents do not cite any regulatory authority for the FDA's oversight of or moratorium on food products from cloned animals. Nor has the Agency provided a policy analysis on its oversight of clones, their progeny, and their products.

## **II. UCS COMMENTS**

UCS applauds the Agency for conducting an apparently exhaustive review of the existing literature on cloned animals, for relying on data that are in the public arena, and for being explicit about the assumptions used by the assessors to address the lack of peer-reviewed studies on the key issues addressed by the risk assessment.

Our major comments on risk documents fall into four areas: the legal basis for the assessment, the need for a national conversation on cloning, the adequacy of the risk assessment and risk management strategies, and the need for labeling.

### **A. The FDA has not conducted an exemplary pre-market safety evaluation of cloned animals and their progeny, because it arguably does not have the authority to compel cloning companies to produce the needed safety studies.**

#### 1. The FDA does not have authority to compel companies to provide safety studies on their products.

As noted above, the FDA's risk assessment on animal cloning is not accompanied by an analysis of its legal authority or the policy implications of potential modes of regulation. This is surprising, as most proposed regulations, policies, and guidance documents issued by FDA and other agencies set forth the Agency's legal authority to act.

Without such an analysis it is difficult to understand how the Agency views its legal authority. Perhaps the Agency is silent on the issue because it prefers not to confront some of the policy

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<sup>16</sup> Animal Cloning: FAQs About Cloning for Consumers. 2007. Online at [http://www.fda.gov/cvm/CloningRA\\_FAQConsumers.htm](http://www.fda.gov/cvm/CloningRA_FAQConsumers.htm).

challenges that result from its vague legal authority to regulate in the pre-market arena key to the oversight of novel food technologies.

The FDA's authority to regulate food animals is found in the Food, Drug and Cosmetic Act (FDCA). Briefly, the FDA provides two general kinds of authority for the oversight of food safety—post-market and pre-market. The post-market authority found primarily in section 402(a)(1) of the act (21 U.S.C. §341(a)(1)) empowers the FDA to seize or remove products from the market, but only after food safety problems are manifest. This authority does not allow the FDA to test food before it goes to market to determine whether or not it is safe. The section of the food law that does provide the FDA pre-market authority, section 409 (21 U.S.C. §348), applies only to food additives. Where section 409 (21 U.S.C. §348) applies, the FDA has authority to require proof of safety and keep products off the market that have not been approved by the FDA.

The Agency has not applied its food additive authority to cloned animals and it is reasonable to assume from the Agency's silence on the issue that it does not intend to do so. The FDA has also decided not to use its food additive authority to regulate transgenic animals, some of which it intends to regulate as animal drugs.<sup>17</sup> In neither case has the Agency provided an analysis supporting its decision. It is possible that the Agency does not want to be bound by the precedent that it established in applying food additive authority to plants. In that case, the Agency applied the pre-market authority to certain genetically engineered crops, those about which "safety questions exist sufficient to warrant formal pre-market review."<sup>18</sup> So far, no such crops have surfaced that have warranted pre-market review, leaving the oversight of genetically engineered crops effectively a voluntary program. The Agency may not have wanted to establish a similarly voluntary program for cloned animals.

But in any case, having failed to devise a policy that considers cloned animals either food additives or drugs, the FDA is left without the authority to compel cloning companies to do food safety or animal health tests to support the Agency's risk assessment of cloned animals. Nor does the FDA have the authority to keep cloned products off the market pending the evaluation of such tests.

## 2. The FDA should confront its lack of authority to regulate cloned animals and their progeny.

Because the FDA apparently lacks the authority under the FDCA to compel companies to do rigorous, well-designed safety tests, the FDA is reduced to combing through the published literature for relevant studies, cajoling companies into doing studies, and doing the best it can. That is exactly what happened here: FDA ended with relatively few peer-reviewed studies designed to address food safety and animal health questions and had to make the best of it.

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<sup>17</sup> According to information provided in a Q&A, but not presented in any formal document, the FDA intends to use the drug laws to regulate those transgenic animals that contain new substances that could be considered drugs (FDA, Question & Answers About Transgenic Fish, available online at <http://www.fda.gov/cvm/transgen.htm>). Although this approach would allow the agency to collect pre-market safety data and keep products off the market during the approval process, it seems a stretch to assert that whole cloned animals can meet the definition of a drug. In any case, the drug provisions of the FDCA lack transparency and are in other ways unsuited for the regulation of novel animal food technologies.

<sup>18</sup> 57 Fed.Reg. 22990 (1992).

*To be clear, the FDA's animal cloning risk assessment relies on inadequate studies because the Agency does not have the authority under law to require rigorous and comprehensive tests.*

*Similarly, the FDA has put in place a voluntary moratorium because it does not have the authority to proactively keep products off the market.*

The FDA apparently hopes that issuing a stand-alone risk assessment that concludes that products of clones and their progeny are safe to consume will make it possible to side-step the issue of its limited legal authority.

We think that this is a misguided approach for two reasons. First, the cloning assessment is inadequate precisely because of the limited authority to obtain comprehensive tests. But, even if the needed tests were available in this instance, the emergence of modern food technologies demands oversight by governments with sufficient authority to bring the best science to the table. FDA should confront its lack of authority squarely and start now to rectify it.

The lack of clear authority in the FDA to oversee the pre-market development is a major deficiency in U.S. law that is becoming an obstacle to those developing the new food technologies of the 21<sup>st</sup> century, and that is a serious concern for consumers.

3. Until FDA can shore up its legal authority, the Agency should not lift its voluntary moratorium on the products of cloned animals and their progeny.

The legal deficiencies in the FDCA are not minor and will require new legislation, a process that could take several years. The legislation would likely cover all animals produced by novel technologies, including genetically engineered animals. Putting novel animal technologies on a sounder legal footing will lead to better decisions about the course and direction of these technologies. During that time, in our view, animal cloning should not be commercialized. Shoring up the FDA's authority is worth the wait.

## **B. A broad national dialogue is needed on the full ramifications of moving forward with food animal cloning.**

1. The broader issues surrounding animal biotechnology should be discussed before the technology goes forward.

The question animal cloning presents society is not simply whether cloned meat and milk are safe to consume but whether animal cloning, considering all of its ramifications, is a technology that should be used widely, or at all, in food animals. The prospect of cloning raises a welter of issues of deep concern to many people, many of which are ethical or moral in character.

The NRC report on animal biotechnology took serious notice of ethical and policy concerns enmeshed in decisions about animal biotechnology. The report makes clear that technologies that affect animals can have impacts on social, political, economic, and religious and spiritual conditions that in turn can affect health and the environment.

Admittedly many of these issues are beyond the statutory scope of the FDA. But that does not end the matter. The FDA cannot isolate itself from ethical and moral issues. The Agency makes judgments in this realm simply by the way it frames issues. But these judgments are not FDA's to make—especially by default. As the lead federal Agency on this issue, FDA needs to help establish an appropriate forum for dialogue about these issues. The dialogue could take a number of forms—listening sessions, workshops, public debates—but to be most effective probably needs to be led from high levels in the government. If there is no place where ethical and moral concerns can be seriously addressed, they will continue to intrude upon and distort decision making by the risk-based agencies like the FDA.

2. Four specific issues that need further discussion are spillover to human cloning, lack of societal benefits, animal welfare, and the relationship to transgenic technologies.

*a. Spillover to human cloning.* Technical advances in the cloning of food animals will be readily transferable to humans, hastening the day that we must confront the ethical dilemma of a human child being cloned. For many people concerned about the use of cloning as an alternative means of human reproduction, the acceleration of the pace of human cloning technology is an unwelcome by-product of food animal cloning.

The fact that FDA considers animal cloning to be just another assisted reproductive technique adds to the apprehension that the animal work will become the slippery slope to human cloning.

*b. Lack of societal benefits.* The framework used by the FDA in its risk assessment fails to evaluate the issue of economic or other purported benefits of animal cloning. This is appropriate in a narrow legal sense, but in the larger debate whether there are benefits to justify the downsides of the technology looms as an important issue. The purported benefits do not appear to be compelling. Cloning does not confer new traits on animals. Cloning only accelerates the transfer of traits, once identified, into production herds.<sup>19</sup> There is no evidence that cloning will move traits like uniform size or more highly marbled meat into the food system more rapidly than existing reproductive technologies, which are already very efficient. Even if the movement were more rapid, it is not clear that it would lead to lower prices or other benefits to consumers or producers. There may be a stronger case to be made for benefits, but so far it has not appeared.

*c. An ethical framework for the consideration of animal welfare issues.* Unless the success rate of animal cloning improves dramatically, commercially successful animal cloning will lead to the production of a large number of malformed, physiologically impaired animals. This raises serious ethical issues with respect to animal welfare,

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<sup>19</sup> CloneSafety.org, the website sponsored by Cyagra, stART Licensing, and ViaGen, Inc., the world's major animal cloning and livestock genetics companies, in cooperation with the Biotechnology Industry Organization, provides three reasons to clone, only two of which concern food animals. These are acceleration of the reproduction of their most productive livestock and minimizing the use of antibiotics because of the reproduction of only the healthiest animals. It is hard to credit the antibiotic benefit in light of the FDA's conclusions on the fragility of perinatal clones.

especially in light of the minimal benefits offered by the technology. A place is needed to construct an ethical framework for addressing these issues. FDA obviated the animal welfare issue by framing it as a comparison between cloning and other ARTs (see Section C.2 below). We believe that approach is unacceptable and that we need a better way to make ethical judgments about animal welfare.

*d. Cloning as an enabling technology for transgenic animals.* The FDA properly excluded from its risk analysis the products of animals that had been both cloned and genetically engineered, on the grounds that the engineering poses risks specific to the novel material introduced into animals to accomplish genetic engineering. But the risk assessment does not mention the role of cloning as a crucial platform for the advance of genetic engineering in animals.<sup>20</sup> The relationship between cloning and genetic engineering should be a part of the national conversation. For some this will be an advantage to moving ahead with cloning; for others, it will be another reason for concern. It is a question that demands discussion.

### **C. The FDA risk assessment is inadequate.**

#### 1. Food safety

UCS appreciates the enormous effort the FDA put into compiling the papers presented in this evaluation. We understand the inherent challenges of whole food testing and proving a negative assertion. We know that risk assessments are constantly faced with the question of how much evidence is enough and what to do with uncertainty. We applaud the FDA's clear explanation of its approach, which acknowledges the use of policy-based assumptions where data are wanting.

Nevertheless, the risk assessment is in our view inadequate to ensure that all clones in all animals at all ages are safe. The literature did not contain large, well-designed, peer-reviewed studies comparing food safety or nutritional aspects of food products from clones and non-clones. As discussed above (Section II.A.1), the Agency did not have the legal authority to compel companies to produce such studies. As the FDA's thorough discussion of risk assessment makes clear, in situations when the science is lacking the risk assessors fill in the blanks with assumptions—assumptions imbued with values and policy agendas. Our disagreements with the FDA are not as much with the science it presents, as with the policy assumptions it uses to fill in where the science is lacking. In our view, the weight of the evidence at this point does not justify the conclusion that all the food products of all cloned animals are safe, especially when that conclusion will allow the unmonitored and unlabeled sale of cloned food animals.

FDA's risk assessment is based primarily on assumptions buttressed by insufficient scientific observations.

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<sup>20</sup> Introducing new transgenic traits through eggs or sperm is challenging because the new genetic elements can be diluted through sexual breeding. With cloning, scientists can introduce the new genetic material into cells in culture and transfer the nuclei to eggs using SCNT. See, for example, a report on transgenic pigs engineered to produce omega-3 fatty acids; the scientists transformed cells in tissue culture and then used nuclei from the cells to produce clones that were transplanted into gilts. Lai, L., et al., 2006. Generation of cloned transgenic pigs rich in omega-3 fatty acids. *Nature Biotechnology* 24:435-436.

The key scientific observation for FDA is that while the vast majority of cloning attempts fail, with most clones being lost before or just after birth, those clones that survive to adulthood appear normal. Starting with that observation, the FDA assumes that the animals are normal and further that normal animals are safe to consume. Other assumptions are that any abnormal animals that might pose a food safety threat would be detected by meat inspectors and condemned at slaughter, and that the sexual progeny of clones, which again appear normal, can be assumed to be safe to consume.

Most of the data available to the Agency to buttress these assumptions are not studies on food composition or food safety but studies showing that clones exhibit traits within the variation seen in normal animals or those produced by other artificial reproductive technologies. Many of these studies demonstrate differences between clones and non-clones but they are usually disregarded as not biologically relevant.

But there are other ways of interpreting the same studies to arrive at different conclusions about food safety. UCS would marshal the data along the following lines: Animal cloning remains a technology in its early stages that still produces primarily debilitated and physiologically impaired animals.<sup>21</sup> Regarding the relatively few animals that survive to adulthood and appear to be normal, there are sufficient differences between clones and non-clones to conclude that they are not normal, or at least not normal enough to conclude that subtle changes do not pose health risks. Although the possibility of such effects is not great, because milk and meat are so widely consumed in the United States, these deserve to be addressed experimentally in well-defined consumption and safety studies done in all species and breeds headed for the market on animals at the ages they are likely to be consumed.

*Peer-reviewed food safety studies are lacking.*

Although the amount of risk assessment data appears to be huge, it in fact contains very few peer-reviewed studies directly addressed to food safety or food composition. According to the FDA, such studies are scarce in cattle because few of the dairy cattle clones are old enough to have been bred and begun lactating, and there are uncertainties regarding the kinds of analyses of milk that could or should be performed.<sup>22</sup> Compositional studies on meat have the extra challenge of requiring the sacrifice of a whole animal to provide samples for analysis.<sup>23</sup> In the three other species, swine, goats, and sheep, there simply are not many groups producing large numbers of cloned animals. As a result, only a handful of studies are available, and even fewer are peer-reviewed.

On milk composition, the FDA presents only five studies from the literature. Three studies were peer-reviewed, one of which was only an abstract.<sup>24</sup> Another study, done by the Japanese Research Institute for Animal Science in Biochemistry and Toxicology, was available only in the

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<sup>21</sup> "...there is some variability between clones and their sexually derived counterparts," Animal Cloning: Risk Assessment, Chapter VII, Summary and Conclusions.

<sup>22</sup> Food Consumption Risks at 52.

<sup>23</sup> Ibid.

<sup>24</sup> Food Consumption Risks at 58-61.

form of a seven-page English translation of the summary. Data are presented from two other studies, Tome et al. (2004) and Welles et al. (2004), which are not included among the peer-reviewed studies.

The single study from the literature that was presented on meat consumption was the Japanese study for which the Agency had only a translation of the summary.

The Agency presented several data sets produced by industry. One on meat composition from Cyagra presented composition data from eleven clones and comparators. These data, although detailed, were not peer reviewed. Similarly, data were presented from studies conducted by the Viagen Corporation, both on swine clones and swine clone progeny. These, too, were not peer reviewed, and were done on relatively small number of animals raised in unusual settings.<sup>25</sup>

There were no consumption studies done on goat or sheep clones or their progeny or cloned progeny in cattle.

In general, the compositional studies presented by the FDA, though few, are reassuring. They show that clones are comparable to non-clones in their gross composition and in many fatty acids, minerals, and amino acid constituents. But this small group of studies falls far short of the solid evidence that would be required to confidently conclude that *all* clones pose no food safety risks. FDA admits as much by providing a long discussion of how to deal with scientific uncertainties in risk assessment.<sup>26</sup> The sweeping conclusions of safety are based on the weight of the evidence approach which incorporates a large number of assumptions.

A better approach would be for the FDA to first decide what kinds of studies should be done to address both nutrition and food safety and then find a way to have those studies done.

The discussion of the nutrition issue and some of the studies that were presented represent elements of this process. Table VI-14, for example, represents a step in the right direction,<sup>27</sup> but the Agency needs to reach out to the nutrition community to make sure that the list is up-to-date. For example, should the Agency be considering the emerging issues of beneficial fats like the omega fatty acids and conjugated linoleic acids (CLAs)?

Once the Agency has identified the nutrition endpoints, it can go about setting standards for tests in terms of sample sizes, sufficient representation across ages, sexes, breeds, and environmental conditions, and then ask that studies that meet those standards be done.

A similar list needs to be produced on food safety endpoints. We appreciate how challenging this can be, but once again the Agency could seek help by convening an outside committee. Among the endpoints might be some mentioned by the Agency in its analysis or done by various researchers, for example, levels of hormones, allergenicity and feeding studies. Again, once the endpoints are agreed upon, the Agency should define standards for well-done studies.

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<sup>25</sup> Food Consumption Risks at 84.

<sup>26</sup> Food Consumption Risks at 79.

<sup>27</sup> Food Consumption Risks at 53.

While such a body of studies, even if well done, would not resolve every doubt, they would put the FDA in a much stronger position than the assumption-heavy risk assessment presented here.

## 2. Animal health and welfare

### *a. More studies are needed to resolve concerns about animal health and welfare.*

Cloning involves the reprogramming of adult nuclei to a state from which they can direct the development of another complete organism. As the literature reveals, the mechanisms for reprogramming adult nuclei are imprecise and not well understood. As a result, animal cloning still has a hit-or-miss character and fails most of the time. The result is animals that are misshapen and physiologically impaired.

The FDA did a good job of collecting and describing the articles in the published and unpublished literature relating to the health of clones and dams in the four target species. But the major finding here, as on the safety issue, is that relatively few peer-reviewed studies have been done. Moreover, most the studies were done on a single species, cattle, a species that exhibits a disturbingly high incidence of malformed and debilitated animals. The data suggest that the technology might have a higher success rate in other species but they come from too few studies on too few animals to be given too much weight. Overall we think the body of studies is insufficiently rigorous and covers too few species, at too few age stages, to draw general conclusions about animal health of clones.

Some of those studies are discussed briefly below.

*Cattle.* The Agency documents an increased risk of mortality and morbidity in perinatal calf clones compared with other ARTs. Many disorders seem to be related to large offspring syndrome (LOS), a syndrome that encompasses, in addition to fetuses or newborns 20% larger than average for the species, clinical signs like weak or absent suckle response, deformities of limbs and/or head, increased susceptibility to infection, enlarged heart, septal defects, and disproportionate organ development.<sup>28</sup>

The incidence of LOS in cloned cows was reported to range from 8 to 100%, with most studies reporting an incidence over 50%.<sup>29</sup> In addition, cloned cows can exhibit a long list of other abnormalities, including musculoskeletal abnormalities, endophyte toxicity, and gastrointestinal problems, although it can be difficult to attribute these conditions to the cloning procedure.<sup>30</sup> According to the risk assessment, cows used as surrogate dams for SCNT-derived pregnancies are at increased risk of late gestational complications such as hydrops and dystocia, complications for which dams are often put down.<sup>31</sup>

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<sup>28</sup> Animal Health Risks at 14.

<sup>29</sup> Animal Health Risks at 16-17.

<sup>30</sup> Animal Health Risks at 22.

<sup>31</sup> Animal Health Risks at 54.

*Swine.* There are fewer studies available on swine than on cattle.<sup>32</sup> A central study indicated that cloned swine have lower birth rates and higher mortalities, and grow more slowly than non-clones. The Agency suggests that there may be other explanations for these adverse outcomes than the cloning process, but it does not seem unreasonable to ask that regulations be based on health studies whose results do not need to be explained away.

*Goats and sheep.* Very few studies have been done on goats and sheep.<sup>33</sup> So far, goat clones do not appear to develop large offspring syndrome (LOS), but more studies are needed to have confidence that goats will never exhibit the syndrome.<sup>34</sup> Data on sheep clones are even scarcer than for goats but do suggest that LOS is a problem. Lamb clones show an increased risk of mortality and morbidity compared with other ARTs.<sup>35</sup>

*Mature and aging clones.* The Agency agrees that insufficient data exist to assess the risk to mature and aging animal clones.<sup>36</sup> The need for such studies is important in light of the tantalizing and still not well-understood impacts of cloning on telomere length, a chromosome feature thought to be associated with aging.<sup>37</sup> In addition, mature clones are the most likely to be consumed.

Overall, the limited data available on cattle demonstrate that the by-product of cloning is a large number of dead or severely damaged clones. Overall the failure rate for the process is much higher than for natural birth (3-5%), and higher even than for other assisted reproductive technologies. Cloning causes adverse health outcomes for both dams and clones.<sup>38</sup>

Based on its evaluation of this data, the FDA concluded in essence that the health of clones is not an issue. We disagree. In addition to interpreting the results in an unacceptable way (see the next section), the Agency simply does not have enough studies to draw sweeping conclusions. As with the food safety issue, the best approach would be for the Agency to determine what studies need to be done, develop the standards for doing such studies, and find a way to get the industry to do the studies before they take their products to market.

*b. A different approach is needed to interpret results of animal health studies.*

The Agency finds that the frequency of malformations is much higher than in the products of normal breeding or other ARTs. But it appears to find the high failure rate acceptable because the same kinds of anomalies are found in animals produced by other ARTs, albeit at much lower rates.

The Agency seems to believe that because these risks are not uniquely associated with cloning, they are acceptable *at any frequency*. But from an animal welfare point of view, the uniqueness

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<sup>32</sup> Animal Health Risks at 47.

<sup>33</sup> Animal Health Risks at 55.

<sup>34</sup> Animal Health Risks at 52.

<sup>35</sup> Animal Health Risks at 53

<sup>36</sup> Animal Health Risks at 55.

<sup>37</sup> Animal Health Risks at 56.

<sup>38</sup> Animal Health Risks at 54.

of the malformations is irrelevant. What matters is how many animals will experience the serious malformations and disorders as a consequence of cloning.

By the Agency's reasoning, any technology that routinely produces malformed animals is acceptable without regard to frequency as long as similar malformations can be identified as low-level outcomes of natural births or other assisted reproductive technologies. We disagree. The frequency of adverse outcomes has to matter.

UCS does not know what level of anomalies is acceptable. We agree with the NRC report on animal cloning that animal welfare issues associated with animal biotechnologies are of "significant public concern, but difficult to assess because they involve professional and ethical judgments." That is why we have suggested in Section IIB above that the FDA should foster a national conversation seeking an ethical framework for making such judgments.

### 3. Genetic diversity

*Narrowing the genetic diversity in the nation's food animal herds is a threat that is not addressed in the FDA's risk assessment.*

Widespread use of a technology that can provide large numbers of genetic copies has an obvious potential to reduce the genetic diversity of the nation's food animal herds. U.S. herds are already operating on a perilously narrow genetic base. About 95% of the nation's dairy cows, for example, now belong to a single breed, the Holstein.

According to Dr. Donald Coover, a veterinarian and rancher who manages SEK Genetics, one of the major commercial attractions of cloning is the ability to *reduce* genetic variation, thereby producing a more uniform product and reducing management costs.<sup>39</sup> "It makes management incredibly easier if you've got a whole bunch of cows that respond to the same nutritional inputs, to the same disease prevention programs, to the same environment in the same manner," Coover said.<sup>40</sup>

He added that through cloning, instead of producing several thousand offspring in the course of his reproductive life (through artificial insemination), *a superior animal could sire several hundred thousand offspring.*<sup>41</sup> (emphasis ours)

Although it may be commercially appealing, the further narrowing of the genetic base of dairy and beef cattle is disturbing to many scientists. More uniformity means more vulnerability to disease and to bioterrorism, issues that deserve discussion and analysis. For example, many livestock pathogens are also human pathogens, and therefore the possibility of increasing susceptibility to some of these organisms may increase the possibility of transmission to humans.

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<sup>39</sup> 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 Food and Drug Administration, Panel 2. 2002. Online at <http://pewagbiotech.org/events/0924/proceedings2.pdf>.

<sup>40</sup> Ibid.

<sup>41</sup> Ibid.

Where increased disease occurs, increased antimicrobial use is also likely, which may exacerbate antibiotic resistance problems for both animal and human pathogens.

We appreciate that these secondary risks are difficult to quantify. Nonetheless, the biological principles behind them are generally understood. And because these risks may result from policy decisions on cloning, they fall under the broad mandate of protecting public health. FDA needs to at least identify and carefully consider these risks in order to move towards developing tools, legal and scientific, to better address this issue. Until these risks are better understood, commercializing clones and their progeny is premature.

#### 4. Behavior changes

*The risk assessment did not look systematically at possible changes in behavior in clones.*

The NRC report noted observations in the literature on increased aggression in cloned mice and suggested that additional studies of cloned livestock are warranted.<sup>42</sup> This view is backed up by a provocative vignette on a TV show, *This American Life*, in March 2007. The show told the story of the painful discovery that Second Chance, the clone of a famously docile Brahma bull called Chance, did not emulate his progenitor, but has been on occasion brutally aggressive. Behavior is an area where subtle epigenetic errors could have dramatic impacts important from both the animal welfare and human handler point of view. The risk assessment cited only a few studies of clone behavior. The issue needs more systematic study.

#### **D. The Risk Management Plan is inadequate to pick up problems in cloning or new risks associated with the discovery of new techniques in animal cloning.**

The risk management plan proposed by the FDA is exceptionally weak. It proposes no continued oversight of the technology, no restrictions on the sale of products, no requirements for additional data, and no monitoring of the food supply. Once the moratorium is lifted, cloning companies will have carte blanche to clone and sell food animals of any species, including poultry and other animals not reviewed in this risk assessment, and put them in the food supply. The public will know only what companies choose to reveal about commercial cloning.

On the food safety issue, the Risk Management plan proposed by FDA consists primarily of informal and voluntary consultations with producers, monitoring of the published scientific literature, and participation in scientific meetings.<sup>43</sup> The Agency also proposes to work with scientific organizations to establish a database on clone and progeny health. These measures are insufficient to manage concerns about cloning in the following ways:

#### 1. The Risk Management Plan does not require cloning companies to inform the Agency of new animal cloning techniques that might pose new risks.

This risk assessment addresses a single animal cloning technology, SCNT. According to the Agency, “significant changes in cloning technology, especially those accompanied by donor

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<sup>42</sup> NRC study at 12.

<sup>43</sup> Risk Management Plan at 5.

nucleus or oocyte treatment regimens introducing new hazards into the overall process, would significantly increase the uncertainty associated with our judgments regarding the degree of risks that could accompany the resulting clones and clone food products... [I]t would not be appropriate to speculate on the...safety of the process from either an animal health or food safety perspective.”<sup>44</sup> If new risks were to emerge, the conclusions of the risk assessment might no longer be valid.

In its risk assessment, the Agency proposes to follow developments in cloning, presumably in order to intervene and, if necessary, conduct a new risk assessment. It proposes to follow scientific development in three ways—by reading the scientific literature, going to meetings, and maintaining informal relationships with cloning companies. It does not propose to require companies to report changes in the cloning technology, because it has no authority to do so. The FDA will rely on companies to share information with it voluntarily.

But there are good reasons to suspect that companies will not want to share their discoveries with FDA. The industry is small and closely held, with a strong incentive to withhold information from the public and competitors.<sup>45</sup> It is reasonable to expect that the information would not be available in the published scientific literature until long after it has been employed commercially. By then it may be too late to avoid new risks.

## 2. The Risk Management Plan has no way to pick up problems in the food supply.

Because the plan does not *require* adverse event reporting or monitoring of the food supply, it is very unlikely to pick up problems with the cloned food.

## 3. The management plan for animal health risks is also inadequate.

In order to minimize the impact of the acknowledged animal health risks, FDA proposes to work with professional and scientific organizations whose missions include ensuring the health of animals to establish animal health assessments and care standards. This is a good idea and should be pursued. But so far, according to the Risk Assessment, none of these groups has criticized the status quo research with clones on animal welfare grounds. We hope that if the success rate improves, professional organizations would be in a position to establish best practices that would insist on techniques that avoid high failure. If failure rates remain high, at some point the technology should be abandoned.

## **E. The food from cloned animals and their progeny should be labeled as such.**

The FDA is not recommending labeling of the products of clones or their progeny because in its view there is no science-based reason to distinguish products derived from clones from the products of conventional animals.<sup>46</sup>

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<sup>44</sup> Risk Assessment: Chapter VI at 88.

<sup>45</sup> According to the industry website CloneSafety.org, Cyagra and ViaGen scientists have cloned more species and a greater total number of animals than any other company or academic institution. Their staff scientists include global leaders in animal cloning and work with the top researchers worldwide.

<sup>46</sup> Animal Cloning: FAQs About Cloning for Consumers. 2007. Available online at

But the FDA does not need science-based reasons to label. Section 403(i) of the Food, Drug and Cosmetic Act 21 U.S.C. 343i requires that a producer of a food product describe the product by a common or usual name... and reveal all *facts that are material in light of representations made or suggested by labeling or with respect to consequences*. The question is not whether the concerns are science-based but whether the information is “material” under the law. We believe that a good case can be made that where a technology is of intense interest to consumers, information about that technology is material in light of representations suggested by labeling. Without such labeling, consumers do not have a choice to avoid foods they do not wish to eat.

There is no doubt that consumers are deeply interested in and wary of foods derived from animal clones. According to a 2007 Pew poll, a strong majority (over 61%) of those Americans who claim to have heard about animal cloning are uncomfortable with it.<sup>47</sup> Such consumers may not want to eat milk and meat from cloned cows or pigs even if they (or the FDA) consider such products to be safe.

For American consumers who enjoy an abundance—indeed an overabundance—of reasonably priced animal food products, the decision to avoid the products of cloned animals is a rational one that can, and in our view should be, accommodated by the FDA. Without labeling, consumers will have no way of knowing whether food comes from cloned animals. The only strategy for consumers who are intensely opposed to consuming cloned animals would be to avoid animal products or choose only organic products.

### **III. UCS’S RECOMMENDATIONS**

#### **A. The FDA should prepare and issue a legal and policy analysis of the statutory authority it has to regulate animal cloning.**

FDA should prepare and issue a legal and policy analysis of the authority it has to regulate animal cloning. If the Agency concludes, as we believe is the case, that it lacks the authority to establish strong pre-market oversight of animal cloning, it ought to say so, and seek the ability from Congress to establish such authority.

#### **B. The FDA should continue the voluntary moratorium on the sale of the food of cloned animals, pending adequate authority to regulate cloned animals.**

The FDA should not have to troll through the scientific literature or cajole cloning companies to obtain high-quality well-controlled studies on food safety and animal health. The Agency should have clear authority to compel such studies. New regulatory authority would be worth the wait because it would likely shore up the regulatory foundation for transgenic animals as well as clones.

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[http://www.fda.gov/cvm/CloningRA\\_FAQConsumers.htm](http://www.fda.gov/cvm/CloningRA_FAQConsumers.htm).

<sup>47</sup> Pew Initiative Finds Public Opinion About Genetically Modified Foods Remains ‘Up For Grabs’ Ten Years After the Introduction of Ag Biotech. 2007. Online at <http://pewagbiotech.org/research/2006update>.

**C. The FDA should obtain more comprehensive, longer-term, peer-reviewed studies on the composition and food safety implications of the products of cloned food animals and their progeny.**

More comprehensive, longer-term, peer-reviewed studies are needed before we conclude that the products of cloned animals and their progeny are safe to consume or that the cloning process does unacceptably affect animal health and welfare.

The FDA should not simply canvass the published literature for such studies. In the case of food safety studies, it should convene a workshop of experts to determine meaningful nutritional and safety endpoints and design rigorous studies. Similarly, the FDA should convene a group of experts (both scientists and ethicists) with an interest in the welfare implications of cloning to determine endpoints and design studies on animal health. Once the studies are completed, they should be submitted, as appropriate, to peer-reviewed scientific journals for publication.

In addition to requiring longer-term, more comprehensive studies, the new assessments should address the potential of cloning to increase the genetic uniformity of the nation's food animal herds and increase our vulnerability to disease and terrorism.

**D. The FDA should delay lifting the voluntary moratorium on the products of cloned food animals until the success rate of producing apparently normal animal clones improves dramatically, to around 90% rather than the currently achievable 0 to 20%.**

The executive summary of the FDA's risk assessment claimed that the frequency of live normal births "appears to be improving, as the technology matures." The FDA should wait until the hoped-for improvements materialize before it clears animal cloning for unlimited use by commercial operators. There is no guarantee that substantial additional progress will be made in the frequency of normal animals, as FDA seems to implicitly assume.

**E. If the FDA lifts the moratorium on the food products of cloned animals, it should develop a system for registering and monitoring such animals and their progeny.**

New information technologies are making it possible to track individual animals through the food system. If the FDA lifts its moratorium on the food products of cloned animals, it should employ such technologies to establish a system for registering clones and their progeny and tracking their movement, production and use in the food supply.

**F. If the FDA lifts the moratorium on the food products of cloned animals, it should develop a system for labeling milk and meat products of clones or their progeny so that consumers have a choice in the marketplace.**

Consumers in the United States have an intense interest in whether cloned animals and their progeny are to be found in our food system. The choice of whether to purchase such foods should be in the hands of individual consumers, not the government or the industry. Consumers will have such a choice only if the foods are labeled.

If the FDA believes that the Food, Drug and Cosmetic Act does not provide sufficient authority for the Agency to require labeling, it should work with Congress to obtain that authority.

FDA should also issue guidance enabling companies who wish to label their products as not derived from cloned animals or their progeny to do so without being required to include a context statement providing the government's view regarding the safety of the foods.

**G. The FDA should ask the White House to sponsor a national conversation on animal cloning.**

Animal cloning raises a number of important issues admittedly outside of the purview of the FDA that are nonetheless entwined in its decisions and activities. Such issues include societal need for animal cloning, the relationship of animal to human cloning, and an ethical framework for considering the welfare implications of cloning technology. The FDA should ask the White House to sponsor a national conversation on these and other issues related to animal cloning.

**H. The FDA should submit its current risk assessment and risk management plan on animal cloning to the FDA's Veterinary Medical Advisory Committee for its review.**

The FDA's Veterinary Medicine Advisory Committee (VMAC) found the Agency's earlier risk assessment and risk management plan lacking in data sufficient to support its conclusions. Although this risk assessment is far more voluminous than the earlier one, the core studies are few in number and do not definitively support sweeping conclusions about health and a hands-off approach to the future of cloning technology. This risk assessment and management plan should be resubmitted to the VMAC for review and evaluation.

UCS appreciates the opportunity to comment on this issue of critical importance to the public and to the future of the U.S. livestock industry. Thank you for considering our views.

Sincerely,

Margaret Mellon, Ph.D., J.D.  
Director  
Food and Environment Program