Comments on the FDA's Draft Risk Assessment on Animal Cloning: Animal Health Risks

Nina Mak, M.S.
Research Analyst
American Anti-Vivisection Society
801 Old York Rd., #204
Jenkintown, PA 19046
Submitted May 3, 2007
Re: Docket No. 2003N-0573

Table of Contents

1. Executive Summary

In the agency's draft risk assessment on animal cloning, the FDA concludes that cloned animals who are older than six months are as healthy as conventionally bred animals. For clones younger than six months, the FDA states that some animals appear to be at an increased risk of health problems, but that no new problems are seen in clones that are not seen in animals produced using assisted reproductive technologies.[1]

However, the FDA's conclusions on the animal health risks posed by cloning grossly misrepresent the nature of the risks that cloned animals face. An analysis of the FDA risk assessment, based on the agency's own stated objectives and methodology, makes it clear that the agency has failed to accurately and appropriately analyze the data, characterize risks, and draw suitable conclusions.

A more valid assessment would conclude that the scientific evidence overwhelmingly demonstrates that the animals involved in cloning are at a significantly increased risk of suffering from any of a variety of ailments, including pregnancy complications, gestational abnormalities, birth defects, physical deformities, physiological impairments, illnesses, and premature death, when compared to animals produced through natural breeding or assisted reproductive technologies. In fact, 91-99 percent of cloned animals do not survive beyond six months. Data on the health of clones who survive to the juvenile period and maturity, as well as on their reproductive function and the progeny they produce, are sparse and inconclusive. Certain findings suggest that these animals are relatively healthy, while many others suggest that there are potential problems and these animals are not "normal." Certainly, no reasonable assurances can be made that adult clones and the progeny of clones do not suffer health risks as a result of the cloning process.

The FDA's draft risk assessment is riddled with problems related to selective reporting of data, insufficient consideration of evidence indicating risks, and inadequate scientific analysis. The FDA must conduct a proper risk assessment that addresses the concerns outlined in these comments, and should impose a mandatory moratorium on the introduction of cloned animals into the food and feed supply in the interim.

Once the FDA has made the necessary changes to the risk assessment, the agency should find that there is a substantial scientific basis for concluding that cloning is not safe for animals, and in fact causes severe animal suffering. The FDA should therefore also recommend that banning products from cloned animals and their progeny is the only appropriate option for protecting animals from the serious and frequent risks associated with the cloning process.[2]

2. Introduction

According to the FDA, the agency has performed this risk assessment "to determine what hazards might be introduced into animals as the result of the cloning process,"[3] "to characterize the resulting potential risks,"[4] and to place these risks "into the context of other assisted reproductive technologies currently practiced in the United States."[5] Overall, then, the FDA states:

> "[T]he question that is asked is whether animals involved in the cloning process are at greater risk for any adverse outcome relative to other assisted reproductive technologies."[6]

On the basis of this risk assessment, the FDA then seeks "to develop risk management protocols commensurate with the identified risks."[7] The FDA, however, falls far short of these goals, and must make several adjustments to its risk assessment and risk management plan before either document can be considered adequate.

The FDA needs to report and analyze data more accurately in order to properly identify hazards and risks that arise from the cloning process. Currently, several important findings are omitted or overlooked, and when evidence is inconclusive, the agency asserts that the cloned animal is healthy while indications of problems are dismissed. The FDA should consider the full weight of all available evidence, including data showing that the health of cloned animals is at risk, and not just those data that support a determination of animal safety. Furthermore, when there are insufficient data to make any meaningful analysis, as is the case for pigs, goats, sheep, aging cows, and the progeny of clones, the FDA should not assert that these animals exhibit no abnormalities, as the data simply cannot say one way or another.

Beyond identification, the FDA's characterization of cloning risks is also seriously flawed and lacking. By the FDA's own definition[8] (as well as that of the National Academy of Sciences 2002 Animal Biotechnology Report[9]), risk characterization involves estimating the severity and likelihood of adverse outcome(s) (e.g., health problems or premature death) occurring once exposure to a hazard occurs. Even the Codex Alimentarius Commission, which sets international food standards with which the U.S. is supposed to comply, has defined risk characterization as an essential component of risk assessment involving "the qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population…."[10] Yet little such characterization occurs in this risk assessment. Risk characterization, in fact, is not even listed as one of the four steps the FDA outlines as constituting the agency's risk assessment process.[11]

The FDA needs to focus its analysis beyond simply identifying or listing the problems that occur in cloned animals, and must consider the *extent* to which these problems occur. The FDA can and should do more than make only generalized claims about the risks that cloned animals face. In addition, when making these statements, the FDA must avoid grossly misrepresenting the nature of cloning risks by claiming that only "some" animals "appear" to be at an "increased" risk.[12] This assessment is hardly appropriate to describe a technology that results in gestational abnormalities, birth defects, serious health problems, and premature death for roughly 91-99 percent of the animals

involved in cloning, compared to the rare occurrence of such problems in conventionally bred animals.[13]

In addition, the FDA should not obscure the risks that are associated with cloning by asserting that the technology is improving over time,[14] giving the inaccurate impression that the problems seen with cloning will basically disappear in the near future. In fact, cloning has had a consistently abysmal success record,[15] and data that have been published since the FDA's risk assessment only serve to strengthen the argument that cloning results in serious health risks for animals.[16] In any case, decisions about risk must be based on the *current* nature of the risks, not a hypothetical future.

Furthermore, though the FDA states that it seeks to know if "animals involved in the cloning process are at greater risk for any adverse outcome relative to other assisted reproductive technologies", the conclusions formed in the RA do not detail the tremendous increase in frequency with which adverse outcomes occur in cloned animals.

The FDA's position, moreover, that "[n]o adverse outcomes have been noted in clones that have not also been observed in animals derived via other ARTs or natural mating…"[17] is entirely misleading and does not properly acknowledge that problems occur in cloned animals at a concerning rate, far greater than anything seen in conventionally bred animals.[18]

Consequently, this risk assessment on animal cloning, with all its attendant flaws in data analysis, is unacceptable and fails to comply with existing national and international regulations governing risk assessment policy. In fact, it would seem that the entire risk assessment was crafted to conform to a pre-determined conclusion that cloning is safe. <u>However, the data, even if not the FDA's analysis, are clear: cloning presents numerous serious threats to the animals involved at a rate far more alarming than ever seen with assisted reproductive technologies. Cloning is not safe for animals.</u>

The FDA must make the changes detailed in these comments if the real and potential risks related to cloning are to be appropriately identified and characterized. This is particularly important to the FDA's decision-making process, including the agency's risk management plans.

As it currently stands, in fact, the risk management plan is entirely insufficient to address the risks that cloning poses to animal well-being. The FDA's proposal to develop standards of care for the animals involved in the cloning process will do little to lessen the frequent and fatal nature of the risks these animals face. Cloned animals have primarily been produced in facilities with extensive veterinary care, and the rate of health problems and premature death is still extremely high.[19] <u>The only way to prevent the serious health risks that cloned animals face, as documented extensively in the scientific literature, is to ban the use of cloned animals and their progeny in the human food and animal feed supply.</u>

In addition to the scientific justification for a ban on animal cloning, the extreme animal suffering, the public's strong opposition to this technology, and the lack of benefit in cloning animals should all lead the FDA to recommend that cloning be banned. Reviewing these additional issues should be part of the agency's process in developing its policy recommendations on cloning. The U.S. Health and Human Services (HHS), the FDA's parent agency, reported that it follows the National Academy of Sciences' (NAS) standards for risk assessment and management.[20] These standards

include the consideration of social, ethical, economic, and political factors.[21] The FDA, however, does not do this.

Even if the FDA deems the consideration of such issues to be outside its purview, the agency cannot ignore that these factors must be addressed. These issues must be publicly discussed and considered by HHS before any decisions by the FDA on animal cloning are issued, and the FDA should place a mandatory moratorium on cloning animals for food in the interim.[22]

These comments will elaborate on the points mentioned here, using each conclusion that the FDA makes in its risk assessment to evaluate how well the agency identified and characterized risks, determined the degree to which existing data addressed questions of animal health, and characterized residual uncertainty. This analysis will demonstrate that the FDA must revise its risk assessment before making any determinations about animal cloning. A more thorough and accurate analysis of the data on cloning is necessary, and the FDA's conclusions must more appropriately reflect the overwhelming and consistent evidence regarding the serious nature of the risks that cloning poses to animal health. An honest, accurate risk assessment is critical to determining the impact that cloning has on animal welfare, as well as food safety.

Once the FDA addresses the issues raised in these comments, the agency should find that animal cloning causes severe animal suffering, and that cloned animals and their progeny should be banned from the human food and animal feed supply.

3.A Bovine Health Risks

There are abundant data detailing the serious health problems and abnormalities that afflict young cloned cows and the surrogate mothers who carry clone pregnancies. The FDA's conclusions about the health risks these animals face need to be significantly amended if they are to adequately characterize the severity and frequency with which problems occur, and not grossly misrepresent the nature of the risks posed by cloning. In addition, the FDA needs to consider the findings that indicate that older clones and their progeny also exhibit some abnormalities, as well as the uncertainty caused by the lack of sufficient data for these animals, rather than assert that cloned cows who survive the neonatal period are healthy and produce normal and healthy progeny with a confidence that is unsupported by the scientific literature. Lastly, the FDA should analyze the available data to draw comparisons between the occurrence of problems with cloning in relation to ARTs, as the data overwhelmingly demonstrate that cloned animals are far more likely than conventionally bred animals to suffer from any of a variety of often fatal problems (Figure 1, see attached).

Analysis of FDA conclusions:[23]

Conclusion 1: Pregnancy loss
"[T]he SCNT process in cattle is associated with increased incidence of early pregnancy loss or later-term spontaneous abortion of clone embryos and fetuses."

Based on the data presented in the risk assessment, this claim is true. However, it does not convey the extent to which pregnancy losses, late-term losses in particular, occur in SCNT compared to ARTs. Given that the FDA's stated objective is to determine if animals involved in the cloning process are at greater risk that conventional animals, the FDA should acknowledge in its conclusions that there is a much higher rate of pregnancy failure and placental abnormalities in SCNT than in ARTs.

Roughly 90 percent of clone embryos transferred into recipient cows are lost during pregnancy. Wells et al. (1999),[24] for example, reported that of 100 embryos transferred in one experiment, 90 percent were lost before calving, and all 16 embryos transferred in a second experiment were also lost. Heyman et al. (2002)[25] transferred embryos cloned from adult somatic cells into 133 recipients, resulting in only nine births (93 percent loss). Wells et al. (2004)[26] found that 87 percent of embryos transferred were not delivered. Panarace et al. (2007)[27] transferred clone embryos into 2466 recipients, resulting in 1242 confirmed pregnancies at Day 30, and only 358 births (85 percent of embryos lost, or 71 percent of confirmed pregnancies lost). In contrast, the FDA states that "producers and veterinarians become concerned when the rate of abortion exceeds 3-5 percent in a [conventional] herd."[28] Clearly, pregnancy losses are much higher with cloning than with conventional methods of reproduction. The FDA should report the studies described above, given their significance to accurately characterizing the risk of pregnancy loss seen with cloning, and the tremendous increase in risk compared to ARTs.

Also of significance, several studies demonstrate that late-term losses are particularly common in clone pregnancies. Of pregnancies confirmed at the end of the first trimester (Day 90-100 of gestation), Wells et al. (1999) reported that 52 percent were lost in the second and third trimesters;

Heyman et al. (2002) reported a 44 percent loss (seven of 16); and Panarace et al. (2007) reported a 38 percent loss (222 of 580). Lawrence et al. (2005)[29], a study not reviewed by the FDA, reported that seven pregnancies were confirmed on Day 50, of which four (57 percent) were lost by Day 255. Another two were deemed to be in jeopardy and were delivered via emergency C-section, but neither survived. In comparison, zero percent of AI or IVP pregnancies were lost late-term in the Lee et al. (2004) study,[30] and overall less than five percent of pregnancies in cattle bred by AI are lost late-term.[31] The FDA should, again, report such findings and note that late-term losses are unique to clone pregnancies.

In addition, the FDA should discuss the implications that an increased rate of late-term pregnancy losses has for the health and welfare of the surrogate dams. The agency only mentions in the data analysis section that early losses "do not pose a hazard to the surrogate dam."[32] Other studies, meanwhile, have reported that late-term losses "expose the recipients [surrogates] to conditions that threaten their welfare,"[33] and early losses mean that surrogates will have to endure repeated hormone treatments and invasive procedures to establish another pregnancy.

To convey a more complete picture of the problems that occur during clone pregnancies (beyond hydrops and dystocia, which are discussed below), the FDA should also note that placental abnormalities are commonly observed, generally leading to loss of the fetus. As the FDA states earlier, but fails to consider in its conclusions, "a major factor contributing to mid- and late-term spontaneous abortion of clones of both embryonic and somatic cell origin is abnormal development of the placenta (Wells et al. 1999; Farin et al. 2001; Chavatte-Palmer et al. 2002)."[34] Moreover, according to Batchelder (2005),[35] while all seven cattle clone placentae studied exhibited abnormalities, none were found in any of nine conventional pregnancies. Wells et al. (1999)[36] also "noted weak or non-existent uterine contractions, poor mammary development and failure to lactate in cattle carrying fetal clones."[37] These findings indicate that there is significant risk of complication for surrogate mothers of cloned cows.

Conclusion 2: Hydrops and dystocia
"Other identified hazards for surrogate dams of bovine clones are hydrops and dystocia. The risk of developing either of these complications appears to be both species- and laboratory-dependent. Not all cases of hydrops in clone-bearing pregnancies develop into a significant complication or threat, but severe hydrops conditions, when not diagnosed early, may result in the death of the surrogate dam and the clone."

According to the FDA, Developmental Node 1 (Pregnancy and Parturition) "examines the causes and frequency of pregnancy complications, and the relative risks to both the female and fetus, using other ARTs for comparison where such data are available."[38] However, the FDA's statement about hydrops and dystocia is misleading because it does not really convey any information about the frequency, severity, or relative risk of these complications except to create the impression that concerns are not significant for clones.

The data presented by the FDA,[39] however, demonstrate that hydrops occurred in 33 out of 118 non-transgenic clone pregnancies (28 percent overall, ranging from approximately 15 percent up to 40 percent in any given study). In comparison, hydrops occurred in only one out of 249 pregnancies (0.004 percent) involving AI, IVP, or ET,[40] and is estimated to occur in only one out 7,500 pregnancies (0.0001 percent) in the general population of cattle.[41] It is clear from these data that

despite any laboratory differences, hydrops occurs substantially more often in clone pregnancies, so frequently that it can hardly be considered the negligible risk that it is for the general population of cattle.

In addition, contrary to the FDA's claim that not all cases of hydrops develop into a serious complication or threat, Wells et al. (2003) report that hydrops caused 18 of 21 pregnancy losses (86 percent).[42] Seven of 13 clone pregnancies (53.8 percent) in the Matsuzaki and Shiga (2002) study required C-section or induction due of hydroallantois, whereas none of the seven AI or IVP controls required such intervention.[43] In the Batchelder (2005) study, the largest clone weighed 71.0 kg at birth (the average birth weight for comparator animals of the same breed was approximately 40 kg), exhibited swelling in the head and neck, and died three days after birth – and this calf was considered to suffer from only "*mild*" hydrops fetalis.[44] Furthermore, while there are instances when surrogate dams were unharmed by the complication, the FDA reports that "most studies that discussed outcomes indicated that dams developing hydrops were euthanized."[45]

The FDA should broaden its focus beyond isolated cases of favorable outcomes so as to avoid obscuring the overwhelming evidence substantiating the frequency and severity of adverse outcomes. A more accurate characterization of the risk would be that *most* cases of hydrops in clone pregnancies develop into serious complications, *often* resulting in the death of the surrogate dame and the clone.

In its discussion on dystocia in the data analysis section of the RA, the agency reports that dystocia increases the risk of several complications, including damage to the reproductive organs of the surrogate dam and emergency C-section, which carries it's own set of accompanying complications.[46] Risks associated with dystocia may be so severe as to result in death or culling of the surrogate dam. Furthermore, the FDA reports that dystocia "was the most influential factor on calf mortality," and "was also associated with high calf morbidity (illness) in a study of 2,490 beef cattle herds (Sanderson and Dargatz 2000)."[47]

According to the FDA, there are little data on dystocia rates in clone pregnancies because clone producers often elect to deliver clones via C-section.[48] This observation, however, is telling in and of itself. Presumably, given a choice, it would be preferable for a surrogate dam to deliver naturally, without assistance, rather than requiring surgery and all its attendant risks. That clone producers often choose elective C-section implies that natural delivery of clone pregnancies are so frequently fraught with complications (such as dystocia) that default intervention has become more sensible and comparatively less risky.

The FDA states, for example, that "[f]or the surrogate dam, LOS increases the incidence of dystocia, frequently requiring human intervention to remove the calf vaginally, or by C-section, due to the inability of the dam to expel the calf without assistance" (Ch V, P.115). Given that LOS is reported frequently in clone pregnancies (see below), it is logical to conclude that the risk of dystocia is great for pregnancies allowed to proceed to term, and for clone pregnancies not allowed to go to term, risks associated with delivery intervention and C-section are likely instead.

In contrast, the FDA reports the risk of dystocia at four to six percent of pregnancies in the general cattle population, including natural and AI bred cattle (Ch V, P.114). In addition, whereas the

majority of clone pregnancies require C-sections, less than one percent of conventional pregnancies require any such intervention.[49]

The FDA needs to amend its conclusions on dystocia to more accurately reflect the severity and likelihood of dystocia occurrence in clone pregnancies. In addition, the FDA must also correct its statement in the Executive Summary that the risk of hydrops and dystocia only "appears" to be increased.[50] The FDA's statement, as it stands, mischaracterizes the nature of the risks that cloning poses to surrogate dams and perinatal clones, as the data clearly indicate that the risk of hydrops, dystocia, and other gestational complications are substantially increased in cloning compared to ARTs and natural breeding. Furthermore, these complications often result in serious outcomes such as death.

Conclusion 3: Large Offspring Syndrome
"Large Offspring Syndrome increases the risk of dystocia, and may be related to the development of hydrops."

This statement must be amended significantly to sufficiently and accurately characterize the risks that Large Offspring Syndrome (LOS) poses to cloned animals. The FDA reports neither the frequency with which LOS occurs in cloned animals compared to conventionally bred animals, nor the majority of the resulting implications for animal health. LOS, in fact, occurs rather frequently in cloned animals and is associated with serious, often fatal complications.

LOS is often, but not necessarily, characterized by excessive birth weight (roughly 20 percent greater than average). In addition, a long list of abnormalities is reported to coincide with LOS, including: deformities of limbs and head; respiratory, cardiac, hepatic, renal, umbilical, and immunologic problems; organ dysfunction resulting in morbidity and often resulting in high mortality; pulmonary abnormalities including immature lung development, insufficient lung surfactant, and failure of the lungs to inflate; cardiovascular abnormalities including patent ductus arteriosus and ventricular defects; delayed time to suckle and stand; hypoglycemia; forelimb contracture; enlarged umbilicus; patent urachus; respiratory distress; pulmonary hypertension; multiple severe organ abnormalities including diffuse fibrosis of the liver, dysplasia of the biliary system, and right ventricle hypertrophy; and bloat.[51]

All of these problems clearly impact animal health, generally requiring extensive medical and surgical intervention, and have serious implications for animal welfare. Poor suckling, for example, "may preclude immune transfer in colostrum-dependent species, resulting in decreased ability to respond to immune challenge."[52] And "Batchelder related failure of passive immune transfer to poor metabolic status and respiratory distress."[53] In addition, "[s]tress associated with dystocia, prolonged labor and emergency C-section birth is a risk factor for large calves (Kato et al. 1998; Kubota et al. 2000)."[54]

According to the data compiled by the FDA,[55] LOS or its related clinical signs occurred in 151 of 294 live-born calves (51.4 percent) resulting from SCNT, compared to 25 of 278 live-born calves (6.6 percent) resulting from AI, ET, or IVF. In fact, LOS occurs rarely or never in animals produced through natural breeding or AI. For the animals for whom data on survival rates were reported, 66 of 164 live-born calf clones (40.2 percent) exhibiting LOS or its related clinical signs

died, compared to zero deaths among two comparator calves. These numbers do not reflect any losses incurred during pregnancy.

According to the data submitted by Cyagra, 18 of 34 clones (53 percent) had birth weights at least 20 percent above breed average (thus fitting the definition of LOS). Of these 18, 12 (66.7 percent) showed other clinical signs associated with LOS, and five (28 percent) died within 48 hours. An additional 55 of 105 clones (52.4 percent) for whom birth weights were normal or unavailable also showed clinical signs associated with LOS, and 12 of these animals (21.2 percent) died within 48 hours.[56]

It is clear that LOS is a significant risk for cloned animals, far more so than for animals produced using ARTs. The FDA must do more than present the relevant data; the agency must also engage in a meaningful analysis and draw the comparisons between cloning and ARTs that it says is its objective. Doing so would illustrate that cloned animals are highly likely to suffer and die prematurely from LOS, arguably a risk never before seen in conventionally bred animals.

Confusingly, the FDA reaches this conclusion at one point in the agency's data analysis, stating that, "[m]ore recent studies in which IVP and SCNT embryos were produced under the same culture conditions reported considerably higher incidences of LOS in fetal and adult cell SCNT-derived calves compared to IVP (Heyman et al. 2002; Chavatte-Palmer et al. 2002; Matsuzaki and Shiga 2002)…."[57] Yet these studies are not included in the FDA's table on LOS incidence in clones,[58] nor does the FDA generally maintain this analysis when discussing LOS risks in clones.

Furthermore, the FDA must not downplay and obscure the risk by claiming in its data analysis that LOS incidence in clones is improving over time. A review of the data compiled by the FDA[59] demonstrates that incidence, in fact, has varied over time, but has not showed any downward trend, and instead has remained consistently high (Figure 2, see attached).

In addition, the FDA should not selectively report data, such as in its claims that the "[r]eported incidences of LOS in peer-reviewed publications on cattle clones have ranged from as low as 1/12 (8.3 percent) (Miyashita et al. 2002) to as high as 12/24 (50 percent) (Kato et al. 2000)."[60] The incidence of LOS in calf clones actually ranges as high as 100 percent.[61]

The FDA's statements in the Executive Summary of the RA must also be amended so as to not mischaracterize the risks posed by LOS. The FDA states, for example, that, "[c]lones exhibiting LOS may require supportive care at birth, but can recover…,"[62] creating the impression that cases of LOS are generally not serious or fatal. In fact, clones exhibiting LOS *often* require supportive care, and have been reported by Cyagra[63] as requiring any of 10 different interventions, including surgery. The FDA even admits as much elsewhere in the RA, stating that "LOS newborns…if they are to survive, often require significant veterinary intervention,"[64] though this analysis is clearly not reflected in the FDA's conclusions. Moreover, while some of these clones recover, many do not, as evidenced by the fact that 42 percent in the Panarace et al. (2007) study died despite receiving extensive veterinary care, and by the high mortality rate (40.2 percent) associated with LOS in general.

Conclusion 4: Neonatal mortality rates
"Neonatal death rates for cattle clones currently average approximately 20 percent."

It is not clear how the FDA derives this figure. Based on the agency's table of survival rates of live-born bovine clones and comparators through the juvenile period,[65] 158 out of 555 non-transgenic clones (28.5 percent) die during the neonatal period. The FDA also reports that Chavatte-Palmer et al. (2004) followed an additional cohort of 58 live-born calves and found that 14 (24 percent) died after the first week following birth.[66]

In addition, in making this statement, the FDA again fails to place the risk in the context of ARTs. From Table V-1, only three of 247 AI-derived calves (1.2 percent), and 77 of 491 IVP-derived calves (15.7 percent) died during the neonatal period. Other studies reported by the FDA cite similar loss rates, ranging from 2.3-14.4 percent for BNT, IVP, ET, and AI calves. Overall estimates from the USDA for beef calf mortality within 24 hours of birth (including still births) is 3.4 percent.[67] For dairy replacement heifers, 1.8 percent of live-born calves die during the first week of life.[68]

Yet the FDA states in Appendix A that "…clones born after a carefully monitored pregnancy under closely supervised conditions are at a slightly increased risk of dying than animals derived via in vitro fertilization, or artificial insemination…."[69] The above data, however, clearly demonstrate that neonatal death rates for cattle clones are greater than 20 percent, and are significantly higher than those seen for animals produced by any other means.

These reported mortality rates, moreover, do not even take into consideration the number of cloned calves who are stillborn. Of the 134 clones from the Cyagra data set, 11 (8.2 percent) were stillborn.[70]

The FDA frequently argues that survival rates for clones are improving as cloning technology matures. The FDA states, for example:

> Early reports, beginning in 1998, of clone mortality rates were 50 to 80 percent (reviewed by Solter 2000). Survival rates have improved in some recent studies, with mortality during the first month of life of approximately 18 percent (21/117; Pace et al. 2002 for a cohort of mixed transgenic and non-transgenic clones) and 20 percent (6/30; Lanza et al. 2001 for a cohort of transgenic cattle), with most of the deaths occurring during the first 48 hours postpartum. Similarly, data supplied by Cyagra, Inc. indicate 22 percent mortality in the first 48 hours (30/134) among non-transgenic clone calves born between 2001 and 2003.[71]

However, this argument is based on selective reporting of data. There are, in fact, several recent studies in the table the FDA is relying on[72] that report far greater than 18-22 percent mortality. Batchelder (2005), for example, reports 75 percent mortality; Chavatte-Palmer et al. (2004) reports 38 percent mortality; Gong et al. (2004) reports 56 percent mortality; Heyman et al. (2004) report 30 percent mortality; and many others. While some of these mortality rates are lower than the 50-80 percent reported by the FDA as associated with early attempts at cloning, they have remained consistently high over time and are clearly greater than 18-22 percent. In addition, none of these rates, not even the FDA's 18-22 percent, should be considered acceptable, as all represent a significant loss of life caused by cloning.

The FDA's analysis of mortality rates in clones suffers from confusion throughout. In the Executive Summary, for example, the FDA claims that, "[a] significant proportion of perinatal clones survives gestation and is born without significant health problems,"[73] but then goes on to state that "[t]he frequency of live normal births appears to be low…."[74] The FDA's statements are clearly contradictory, and the FDA must clarify its analysis of the data. Specifically, the FDA needs to correct the numerous instances in which it underrepresents the high rate of mortality seen in clones, as a significant proportion of perinatal clones *is* born with significant and fatal health problems, and an even greater proportion *does not* survive gestation.

Premature death is, obviously, a serious risk that greatly impacts animal welfare, and when it occurs for at least one quarter of a population, it represents a unique concern and should be appropriately characterized as such by the FDA.

Conclusion 5: Factors influencing calf mortality
"Dystocia may be the most influential factor on calf mortality, due to trauma or difficult labor and emergency C-section; however, abnormal organ and musculo-skeletal development also appear to play important roles."

This claim attempts to describe major causes of mortality in calf clones, but does not do so accurately. The FDA should mention the frequency with which such problems occur and the severity of those problems. In addition, to properly characterize the risks faced by calf clones, it is important for the FDA to report not just what causes death, but also how often calf clones die.

A review of the data shows that, "[d]ystocia and related morbidity and mortality of the young animals are *common* in cases of LOS when C-sections are not planned [emphasis added]."[75] Furthermore, "abnormal organ and musculo-skeletal development" is often attributed to LOS, and LOS occurs frequently in clones and often results in death (see above). The FDA's statement should be amended to reflect the relationships between LOS, dystocia, and abnormal organ and musculo-skeletal development.

In addition, the phrase "abnormal organ and musculo-skeletal development" should be elaborated upon to more accurately convey the serious and diverse nature of problems seen in calf clones, which include limb deformities, fatty liver, anemia, degenerating kidneys, respiratory failure, etc. Furthermore, "appear" should be stricken, as the term is hardly an accurate description of the evidence available on this topic, given the numerous studies identified by the FDA reporting such abnormalities in clones who die during the neonatal period.[76]

With regard to how often calf clones die, from these or other causes, please see below.

Conclusion 6: Juvenile mortality
"Three calves generated by Cyagra, although surviving the early neonatal period, died during the juvenile period due to either congenital abnormalities or failure to thrive."

This is the only statement about juvenile health that the FDA makes in this section on bovine health risks. As such, it implies that the only evidence of health risks in juvenile clones is an isolated report

of three deaths. The FDA, in fact, states in the Executive Summary that, "[c]lones in the juvenile to prepubertal age cohort do not appear to be at an increased risk of morbidity or mortality….Most animals surviving the neonatal period appear to grown and develop normally [emphasis added],"[77] providing further indication that the FDA is claiming that juvenile clones are essentially healthy.

However, a long list of health problems and abnormalities (including those contained in the statement above about abnormal organ and musculo-skeletal development) and several reports of death in the juvenile period can be identified in the scientific literature.[78]

The calf clones in the Cyagra data set, in fact, suffered from a "much higher rate" of health difficulties, such as umbilical problems and contracted tendons, compared to non-clones.[79] According to the USDA, the rate of illness in the general population of beef replacement heifers from weaning to puberty is "very low."[80] The FDA even acknowledges that the increase in umbilical problems seen in clones "represents a real risk to clones,"[81] and should indicate this concern in its conclusions.

Of particular concern is that even cattle clones who appear healthy have been reported to die unexpectedly at some later time. The FDA, in fact, cites *five* different studies that report such a finding in its 2007 article published in *Theriogenology*,[82] but does not mention this in the risk assessment. At least one other study not included in the FDA's assessment (Lawrence et al. 2005[83]) also reports the sudden and unexpected death of a nine-month-old clone who was asymptomatic. The FDA must correct this oversight and consider the implications of such frequent reports of sudden death in apparently healthy cattle clones.

In addition, Chavatte-Palmer et al. (2004) reported that six of 44 clones (13.6 percent) died between the perinatal period and six months of age,[84] while Batchelder (2005) reported that three of six clones (50 percent) died or were euthanized during that same period.[85] In comparison, none of the nine comparators in the Batchelder 2005 study died, and the USDA reports that only 2.4 of naturally bred or AI-produced dairy replacement heifers die between weaning and calving.[86]

Additional data are also presented by the FDA that indicate potential further abnormalities with juvenile clones, but the FDA needs to examine the significance of its findings. For example, eight clones in the Batchelder (2005) study displayed periodic moderate or severe hyperthermia for 60 days.[87] The cause of the hyperthermia could not be determined, the calves showed no signs of illness, and the condition was unresponsive to treatment. The clones also showed differences in weight gain compared to their breed-matched controls. A group of 10 clones in the Chavatte-Palmer et al. (2002) study also exhibited a case of hyperthermia similar to that reported in Batchelder (2005), but none of the AI controls did.[88] Three clones in the Cyagra data set had lower levels of gamma glutamyl transferase (GGT), and three other clones had lower levels of sorbitol dehydrogenase (SDH).[89] Govoni et al. (2002) noted differences in GH, IGF-1, and IGFBP3 levels between clones and controls, and in their response to GHRH.[90]

Yet the FDA discusses the significance of none of these finding, other than to say that no health problems could be detected in the clones that could explain the findings. Rather, the uncertainty as to the significance of these differences, due to the limited data on the subject, is used to dismiss any potential concerns entirely. Perhaps these findings are indicative of an undiscovered problem with clones, or perhaps these differences have an as of yet unrecognized consequence. The FDA should

acknowledge this uncertainty, as the agency is supposed to do as part of the risk assessment process, rather than selectively omit such findings in its conclusions.

Similarly, other differences noted in studies of clones in the juvenile period need to be more seriously considered rather than explained away as resulting from differences in management practices. For example, bloat and other gastrointestinal problems have been reported in clones in several studies (Wells et al. 2004, Cyagra 2003, Batchelder 2005), but these findings were dismissed by the FDA because these problems "can also result from poor feeding/grazing management."[91] "A few clones" in the Cyagra data set exhibited elevated levels of growth indicators, such as calcium, phosphorous, and alkaline phosphatase, relative to comparators. The FDA, however, states that "these differences may be attributed to differences in management."[92] While management practices may be the cause of these findings, this is not necessarily so. Since the data do not clarify the matter, the potential for risk cannot be dismissed entirely.

In other instances, the FDA needs to more thoroughly analyze the data on clone health. For example, the FDA presents unpublished data on hematology and clinical chemistry values for three bull clones, and finds that "[m]ost variables measured were within the reference range."[93] The FDA should, however, also evaluate whether the clone values tended to fall in a particular part of the range, as this may be indicative of a trend with health implications, rather than just normal variability.

The Cyagra data set revealed that blood glucose values for six of 42 clones were higher than for comparators.[94] Since glucose levels were not elevated in the clones' urine, the FDA attributes the high blood levels to a transient response to stress. However, even if this is so, the FDA should question why the clones would have an elevated stress response compared to non-clones, as this has implications for their long-term health.

A more appropriate characterization, then, of the risks that cloning poses to juvenile clones would be as follows: An accurate review of the data shows that juvenile clones are known to face numerous serious health risks, including a risk of premature death, at much higher rates than conventionally-bred animals. These problems are rare in the general population of cattle, but occur frequently in clones. It is uncertain whether juvenile clones also face additional, undiscovered health risks, as the data are insufficient to draw any reliable conclusions about the matter.

Conclusion 7: Reproductive health
"The limited data suggests that there are no adverse health effects on the reproductive health of cattle clones, although this tentative conclusion must be tempered by the small number of available studies. Only one report of apparent reproductive failure in a female Holstein heifer clone has been published."

The FDA accurately points out that little data are available to assess the reproductive health of clones, but grossly mischaracterizes the data that are available. There are, in fact, several indications that cloning may have an adverse impact on reproductive health. The FDA needs to be more forthcoming about these findings, must evaluate the significance of these findings, and must take them into consideration when making a conclusion about the reproductive health status of clones.

A study by Enright et al. (2002), for example, found that heifer clones "reached puberty at a later age than [AI-derived] controls (314.7 ± 9.6 days vs. 272 ± 4.4 days), and had higher body weights at first estrus (336.7 ± 13 vs. 302.8 ± 4.5 kg)."[95] The FDA argues that the age and weight of the clones may have been under genetic control, and thus not a concern. However, given that no records were kept for the donor cow, the cause of the abnormal findings cannot be determined one way or another. Therefore, the findings cannot be dismissed, and should be kept in consideration as a potential indication that cloning may affect reproductive health. In addition, as the FDA points out, one of the 4 clones (but none of the controls) failed to become pregnant after AI. The FDA should consider the potential significance of this finding.

A recently published study by Heyman et al. (2007),[96] which is not included in the risk assessment, also found that clones reached puberty significantly later than conventional calves (+62 days). This finding reinforces the observations in the Enright et al. (2002) study, supporting the possibility that reproductive maturity is somehow altered in clones.

Only two studies were identified by the FDA as reporting the rate of pregnancy in non-transgenic clones. From these studies, the pregnancy rate for clones was 28/34 (82 percent), compared to 90-95 percent for comparators.[97] This may reflect reproductive difficulties in clones, or additional data may make the average closer to that seen in conventionally bred animals. The FDA should have engaged in this level of analysis.

Given the scant data available to make any definitive statement about reproductive difficulties in cow clones, the FDA should have taken into consideration some of the data that have been obtained from mouse clones. The FDA notes in Chapter III, for example, that, "[o]f the 25 animals [i.e., mice] studied…two female clones delivered only one litter and then became sterile for unknown reasons."[98] Such data strengthen the possibility that clones are not reproductively normal, and further raises the possibility that observing just one round of reproduction in clones may not be sufficient to identify problems.

There are numerous additional instances when the FDA needs to be more forthcoming about data that indicate that reproduction in clones is perhaps not as normal as in conventional animals. For example, in its analysis of the study by Shiga et al. (2005), the FDA notes that "ejaculate volumes were similar between two bulls (2.34 and 2.67 mL) but were lower than the range for conventional Black bulls (5-8mL)."[99] Yet the significance of this finding is not discussed, and despite the fact that it suggests that clones may not have normal reproductive function, the FDA treats the data as if no differences were found.

In that same study, the FDA reports that two of 12 pregnancies to a bull clone ended in spontaneous abortion in mid-pregnancy, compared to five spontaneous abortions out of 64 pregnancies by the nuclear donor. The FDA should also report these data as percentages, which would reveal that the abortion rate for the clone is 16.7 percent, compared to 7.8 percent for the donor. Given such a difference in abortion rate, the FDA should acknowledge that these data are noteworthy.

The FDA also reports that five of 37 pregnancies to a clone bull in the Tecirlioglu et al. (2005) study were lost between 30 and 240 days of gestation, compared to two of 40 pregnancies to the donor bull.[100] The FDA states, misleadingly, that these pregnancy losses are "similar." However, five of

37 translates to a 13.5 percent loss rate for the clone, compared to two of 40, which translates to a 0.05 percent loss rate for the donor. These are hardly similar values. Given such differences in abortion rates, it would seem difficult to say that, "there are no adverse health effects on the reproductive health of clones."

The FDA reports another study, Heyman et al. (2004), which compares sperm characteristics of three clones to the donor bull.[101] According to the FDA's analysis, none of the characteristics (percent normal sperm, cleavage rate, and blastocyst rate) were statistically different between the donor and the clones. However, looking at the data presented in Table V-10,[102] the clones have consistently lower values than the donor. While these differences may not have achieved statistical significance, perhaps due to the small sample size, the FDA should make note of the trend and its potential implications.

The Heyman et al. (2004) study also found that the single clone bull studied was able to inseminate 41 of the 63 females used for AI (65 percent). Two of the 41 pregnancies (five percent) were lost by day 90 of gestation. Of the 26 pregnancies allowed to go to term, one pregnancy (four percent) resulted in a premature stillborn. The FDA should compare these rates to those observed with the nuclear donor used as a comparator. In addition, to be more informative, the FDA would be more appropriate to compare the clone's rate of AI pregnancy loss to that seen in general with AI, not IVF.

Reports on semen evaluation for 4 bull clones (unpublished data)[103] would also benefit from more accurate characterization and appropriate analysis. Values for semen volume, concentration, and percent normal sperm are presented for the clones and compared to normal reference ranges. One bull clone was far below normal, but the FDA only says that "he likely would have failed a breeding soundness exam," and does not discuss any concerns that arise from the finding of such an abnormal clone. Another clone was slightly below normal, but the FDA describes this clone as "marginal." The FDA characterizes the other two clones as having "acceptable semen," even though values for these clones were either below normal or on the very low range of normal. Reviewing the data, it would be difficult to say with any confidence that any of these clones are really normal (Figure 3, see attached). The FDA should reconsider this evidence and the uncertainties raised by the data and make a more accurate assessment of the reproductive health of these clones.

Similarly, the FDA reports that "semen quality measurements on two of the clones [in Galli et al. 2003, unpublished data]…were also considered within the normal range for young bulls."[104] However, three of the 4 values presented (average volume and concentration for two bulls) were actually below normal and the remaining value was on the very low end of normal.

In addition, the FDA never fully addresses the report of a clone who "gave birth prematurely to a stillborn calf, did not have complete udder development, and produced approximately 30 percent less milk during her first lactation compared to her clone mates."[105] It appears that the FDA instead selectively focuses on the findings and anecdotal reports that suggest that adult clones have normal reproductive function, ignoring the evidence that could discredit such a claim.

With regard to determining the sufficiency of the data to answer questions about the reproductive health of clones, the FDA is again misleading in its analysis. The agency claims that, "[d]ue to the complexity of the reproductive system, careful attention was directed to reports of puberty and

reproductive function in clones to determine whether cloning had perturbed this delicately balanced system."[106] However, with such little data available on the topic (most studies providing primarily anecdotal accounts), it does not seem that there is sufficient evidence to reach convincing conclusions about a question that the FDA considers so important.

Yet the FDA expresses little uncertainty in its assertions that cloning does not pose any risks to the reproductive health of clones. The FDA states, for example, in the Executive Summary of the risk assessment that:

> "Data on reproductive function in cows or bulls of this age cohort [adults] indicates that healthy bovine clones surviving to reproductive maturity function normally and produce healthy offspring. These data are consistent across studies. …the observation of normal reproductive function provides an additional degree of confidence to the conclusion of the appropriate development of these animals."[107]

However, as the above analysis demonstrates, studies *do not* consistently demonstrate normal reproductive function in clones. Many studies, in fact, suggest just the opposite. The data are simply insufficient to describe the nature of clones' reproductive health accurately. However, there are enough data that indicate that potential problems may exist, making the FDA's conclusions far from an accurate characterization of the risks that adult clones may face. A more accurate assessment of the data, then, would indicate that the data are inconclusive but some evidence for reproductive health problems in clones does exist.

Conclusion 8: Post-pubertal maturation and aging
"Data on post-pubertal maturation and aging indicate that as surviving clones approach maturity, they experience fewer health problems and are physiologically similar to non-clone comparators."

In making this assertion, the FDA fails to describe the limited nature of the data on mature and aging clones, fails to accurately characterize the risks that older clones may face, and also fails to convey the uncertainty of the findings. Instead, the FDA creates the misleading impression that the data conclusively show that older clones are generally healthy.

In actuality, "there are limited data on concerns related to aging and longevity of conventionally-derived cattle,"[108] and these issues "have not been studied extensively due to the relatively short time that cloning has been practiced."[109] It is thus difficult to assert anything about the health of these animals with confidence. The question of premature aging and shortened telomeres, for example, is difficult to resolve, as "convincing data on clones"[110] are not currently available and "most clones have not been alive for the full 'natural' lifespan of their species."[111] In addition, the little data that are available do not present a clear picture of the health status of clones as they age.

In the Chavatte-Palmer et al. study, for example, two of 38 clones (5.3 percent) died following the juvenile period.[112] Batchelder (2005) also reported a sudden death of a clone at 25 months.[113] Necropsy findings revealed that the clone had severe trace mineral deficiency. Wells et al. (2004) reported that 17 of 89 clones (19 percent) who survived to three months of age did not survive post weaning.[114] Numerous causes of death were reported in the Wells et al. (2004) study, including musculo-skeletal abnormalities, anemia, organ dysfunction, and disease.

The Wells et al. (2004) study also found that several hematology and clinical chemistry values were different for nine clones when compared to nine non-clones.[115] The FDA should address the significance of this finding, rather than dismiss it by noting that the clone values still fall within the published reference range. After all, comparing values between animals who are raised in identical environmental conditions under identical management systems (i.e., contemporary comparators) is far more informative than comparing values to a reference range. That differences were noted between clones and their contemporary comparators is a finding of concern, one that certainly does not lend support to the conclusion that adult clones are similar to non-clones. In addition, the FDA should consider whether there may be health implications if blood values for clones are consistently different than average, even if they are still within the normal range.

Conclusion 9: Mortality in older clones
"Among older clones that die or are euthanized, health problems appear to be related to pre-existing conditions (musculo-skeletal defects, GI tract problems) already identified during the perinatal and juvenile periods."

This statement is true, but does not consider the potential health problems indicated by the studies discussed above. If the FDA had properly considered the findings reported in these studies, the agency may have found evidence for the possibility of new and additional health problems in adult clones.

Conclusion 10: Progeny
"Progeny of cattle clones do not exhibit LOS, and appear to grow and develop normally."

The FDA's conclusion about the progeny of bovine clones is stated with a certainty that is unsupported by the limited data available on these animals. Aside from anecdotal reports, the FDA reports only four studies concerning cattle clone progeny, and these studies provide very little information about only a few animals. In many cases, the progeny in a study are from only a single clone. With such little information available, the FDA should revise its conclusion to reflect the fact that any statement about the health and normalcy of cow clone progeny is speculative at best.

In addition, the largest study (Wells et al. 2004, of 52 progeny of clones) found that several (eight of 28) hematology and clinical chemistry values were different between clone progeny and their comparators. As with similar data reported for mature and aging clones, the FDA should address the significance of this finding, rather than dismiss it by noting that the clone values still fall within the published reference range. After all, comparing values between animals who are raised in identical environmental conditions under identical management systems (i.e., contemporary comparators) is far more informative than comparing values to a reference range.[116] That differences were noted between clones and their contemporary comparators is a finding of concern, one that certainly does not lend support to the conclusion that the progeny of cattle clones are normal. In addition, the FDA should consider the significance of the greater variability seen in the values for the progeny of cattle clones compared to that seen for the comparators. In particular, it would be more informative to look at values for individual animals, rather than averages, to see how many individuals have abnormal blood parameters that may be indicative of underlying health problems.

Ortegon et al. (2007)[117] recently published a study on the progeny of cloned cows, which is not included in the risk assessment. In this study, the progeny were found to have decreased temperature, heart rate, and respiratory rate, but most other parameter were reported as normal. However, this study examined only seven of the 30 progeny who were produced, and no explanation was given for how or why those seven were selected. In addition, the data were simply too variable for some of the parameters measured to ever be able to indicate statistically significant differences, particularly with such a small sample size. Thus, even with this new study, information is still largely lacking on the health of cloned cow progeny.

Additional information FDA should consider

There are several additional findings that the FDA should consider and incorporate into its conclusions to provide a more complete and accurate characterization of the risks that cloned cattle face.

For example, neonatal clones from Chavatte-Palmer et al. (2002)[118] and the Cyagra data set[119] exhibited differences in body temperature, plasma leptin, thyroxine (T4), IGF-II, AST, GGT, cholesterol, and bile acids compared to conventionally bred controls. The significance of these differences has yet to be explained, and the potential for concern cannot be ruled out.

In addition, numerous abnormalities have been found in neonatal clones that have not been mentioned in the FDA's conclusions. From Chavatte-Palmer et al. (2004)[120] and the Cyagra data set,[121] neonatal clones have been reported to have fatty liver, degenerative kidneys, or ascites (abnormal fluid accumulation), or to be more susceptible to infection. Heart rates for clones from a commercial cloning company[122] were also more variable than rates reported for conventionally bred animals, a finding which the FDA does not discuss, but which may indicate underlying deficits in clone health or ability to handle stress. Such findings add further weight to the evidence that neonatal clones are simply not normal and face a great many serious risks that threaten their welfare.

Also of importance is the fact that many clones have appeared healthy but have later been found to have underlying abnormalities which had gone undetected. The clones in Chavatte-Palmer et al. (2002), for example, appeared normal and healthy, but displayed significant differences in certain blood and hormone values.[123] The authors also reported that one apparently normal clone fetus had small kidneys,[124] and later reported (in Chavatte-Palmer et al. 2004) that three clones "died suddenly with few or no clinical signs."[125] Batchelder (2005) also reported that a seemingly healthy clone died suddenly at 25 months.[126] The necropsy revealed that this animal had severe trace mineral deficiency. In Lawrence et al. (2005),[127] a study not reported by the FDA, one clone died suddenly and unexpectedly at nine months of age. The clone displayed no symptoms of illness, but was diagnosed with acute enterotoxemia post mortem. Such findings raise serious doubts about any claim of apparent health in a clone.

Of particular relevance to the discussion of the risks associated with cloning is the fact that the overall mortality rate, measured as the number of transferred cloned embryos that fail to result in a live cow who survives birth and the neonatal period, is extremely high, generally greater than 95 percent. The FDA, however, fails to discuss this issue at any point in the risk assessment. Clearly,

when a technology results in death and deformity for such a massive number of animals, the risks must be considered significant and should not be omitted from the FDA's consideration.

The scientific evidence demonstrating that cow clones are at serious risk of suffering severe health problems and premature death is bolstered by articles which were recently published in the journal *Theriogenology* but which are not included in the risk assessment. Panarace et al. (2007),[128] for example, reported a cloning study conducted by Cyagra in which 89 percent of 3374 clone embryos died during gestation. Of the remaining 388 calves, 18 percent died at birth, meaning 91 percent of the transferred embryos failed to result in a live-born calf clone. Fifty four percent of the pregnancies necessitated C-section for delivery, with another 30 percent requiring non-surgical intervention. Of the clone calves who survived birth, an additional 42 percent died within the first 150 days, despite extensive veterinary supervision and care. Antibiotics were given to a full 75 percent of cloned calves. A long list of abnormalities was reported for the cloned animals, including those already mentioned.

Such findings demonstrate that cloning poses serious risks to the health of the animals involved, and these risks are not lessening with time. The FDA needs to consider the full weight of all the available evidence of adverse outcomes in cloned cows; the concerns raised by differences in clones which cannot be explained; and the implications of apparently healthy animals who have underlying abnormalities or who die suddenly.

3.B Swine Health Risks

Published reports of cloning attempts in pigs demonstrate that the process is extremely unsuccessful, failing more often than in most other species. As a result, few cloned pigs exist to study, making it difficult to make any convincing statements about the health of these animals. The FDA should therefore not conclude that cloned pigs are healthy when the scientific evidence is lacking to support such an assertion. The FDA should also decrease its reliance on isolated reports of normalcy, and give fair consideration to the troubling findings that have been reported in the few studies that do exist. By making these changes, the FDA's conclusions regarding pig clone health will be a more accurate characterization of the available data and will suffer from substantially less bias in interpretation.

Analysis of FDA's conclusions[129]

Conclusion 1: Pregnancy and parturition
"Swine carrying clone pregnancies do not appear to experience hydrops and dystocia."

As the FDA's only statement about pregnancy and parturition risks for swine carrying clone pregnancies, this conclusion is misleading and does not incorporate the findings that consistently show significant fetal loss during pregnancy and overall low pregnancy success.

According to USDA statistics, the average litter size for conventionally bred swine in the U.S. in nine piglets (range 7.5-9.2).[130] Each of the clone studies cited by the FDA, however, report significantly smaller litter sizes for swine carrying clone pregnancies.

Betthauser et al. (2000), for example, reports the birth of only two live piglets in each of two litters,[131] and Onishi et al. (2000) reported the birth of only a single clone pig.[132] According to unpublished data reported by the FDA, a cloning company was able to produce only five piglets from two litters.[133] Polejaeva et al. (2000) reported the birth of five clone piglets in a single litter,[134] compared to an average litter size of 10.9 for comparator pigs in the same study under natural mating conditions.[135]

Given that, "in swine, a litter-bearing species, at least four viable embryos are needed during early gestation for the sow to carry a pregnancy to term,"[136] but less than four clones were delivered in five of the six pregnancies carried to term in the studies above, it is evident that the rate of fetal loss is high in pig clone pregnancies. This rate, moreover, is far greater than the 9.2 percent loss seen among conventionally bred swine.[137]

In addition, these studies report further evidence of pregnancy-related failures of cloning attempts in pigs, which the FDA should have included in its risk assessment. According to Betthauser et al. (2000),[138] at least another two pregnancies were aborted, resulting in zero live births. (The status of the remaining three pregnancies that the authors were able to initiate was reported as pending in the study.) These births, moreover, required the transfer of 100-300 clone embryos plus an additional 100 embryos produced through in vitro fertilization into each of 23 recipients.

The single birth in Onishi et al. (2000)[139] followed the transfer of 110 clone embryos among four recipients. According to the study, but again missing in the FDA's report, the authors conducted two additional experiments in which zero of 96 and zero of 63 clone embryos transferred resulted in a birth. Overall success rate, then, is one piglet from 269 embryos transferred (0.37 percent).

Polejaeva et al. (2000)[140] (but again not the FDA) reported that, in total, 586 clone embryos were transferred among 10 recipients, resulting in just two pregnancies, one of which was lost and one of which produced the five clones. Overall success rate in this study, then, is five piglets from 586 embryos transferred (0.85 percent).

These studies clearly demonstrate that cloning in pigs is extremely inefficient and unsuccessful. The rate of pregnancy initiation is low, particularly compared to more conventional methods of production. Just two pregnancies were initiated from 10 attempts (20 percent) in the Polejaeva et al. study, and seven pregnancies were initiated from 23 attempts (30 percent) in the Betthauser at al. study, compared to 10 of 19 (53 percent) for IVF by the same authors. In addition, fetal loss is high in the few pregnancies that do occur, resulting in total loss of the pregnancy or significantly smaller litter sizes than average for the pregnancies carried to term, despite the high number of embryos used.

The FDA should report these findings and consider their significance in the risk assessment to more accurately characterize the effects that cloning has on pregnancy and parturition in swine. Initiation and support of clone pregnancies in swine, as well as recovery of donor cells and oocytes in certain cases, requires significant hormonal treatment and surgery. When the number of live births as a percentage of total embryos transferred is far less than one percent, as the above studies demonstrate, the cumulative impact of cloning attempts for the animals involved in the procedures cannot be ignored.

Conclusion 2: Neonatal health
"With the exception of one pig clone born with anal atresia, no other reports of frank deformities have been noted for this time period in non-transgenic swine clones, although birth weights may be lower in swine clones relative to non-clone comparators."

The FDA should qualify this statement by noting that very few studies exist on the health of neonatal pig clones, and most of the evidence that is available is anecdotal in nature. In total, according to the FDA, there are only 49 live-born swine clones from approximately 12 clone lines for whom there could be data in the peer-reviewed literature, and seven more clones from two cell lines in the unpublished Viagen dataset. This is hardly an adequate sample size to determine the likelihood of an adverse outcome occurring, particularly when there is little hard data to evaluate.

Indeed, the majority of the evidence that the FDA bases its conclusions on comes from anecdotal reports that pig clones appeared healthy. Such reports, however, are not particularly informative, as cloning researchers generally believe that although clones may appear morphologically normal, most contain abnormalities from faulty epigenetic reprogramming that "may or may not be manifested in an obvious phenotype."[141]

Birth weight, in fact, is the only measurement which is consistently reported in pig clone studies, and this is overwhelmingly reported to be lower in swine clones relative to conventionally bred comparators. Polejaeva et al. (2000), for example, found that the average birth weight of clones was 25 percent lower than the average birth weight of non-clones of the same line, and Walker et al. (2002) reported that their 26 surviving clones were small at birth.[142] The FDA notes that "similar reports of low birth-weight pigs have been recorded by other researchers."[143] In addition, the seven neonatal swine clones from the Viagen dataset were 35 percent smaller on average than AI comparators.[144]

While little data exist on neonatal pig clones, the data that are available consistently demonstrate that pig clones are highly likely to be smaller at birth than conventionally bred pigs. The FDA's statement that birth weights *may* be lower in swine clones relative to comparators is not an accurate assessment of the available evidence on this subject and needs to be modified. In addition, the FDA should evaluate the potential implications of low birth weight in pig clones, and should also amend it conclusion so as to not create the misleading impression that there is substantial data demonstrating the health and normalcy of pig clones.

Conclusion 3: Mortality rates
"The single study reporting high mortality rates in non-transgenic swine clones reported clinical signs that may be related to various causes, including infectious disease, which cannot be ruled out based on the available data."

In making this statement, the FDA effectively dismisses the findings of this study (Park et al. 2004a and 2005)[145] simply because infectious disease cannot be ruled out. In actuality, the possibility that cloning caused the high mortality rates and severe health problems in the pigs of this study also cannot be ruled out, and this study should be taken as evidence that cloning *may* or *may not* pose serious risks to neonatal pigs.

In addition, there is some evidence supporting the possibility that cloning, rather than infectious disease, was the root cause of the problems seen in the pigs. None of the comparator pigs, for example, were reported as exhibiting health problems or signs of infection, so it seems that something about their clone status jeopardized the health of the piglets. Some of the pigs who died were also reported as having been born weak, which may have predisposed them to an infectious disease, a fact which the FDA acknowledges. However, the FDA does not consider what may have caused the weakness in the first place, or why the weakness was isolated to pig clones.

The FDA's conclusion about the significance of this study needs to be more balanced, rather than taking advantage of uncertainty to dismiss the findings entirely. The fact that one of the largest studies on pig clones reports such troubling outcomes should be a source of concern motivating further inquiry.

Furthermore, in the interest of completeness, the FDA should also report that two of five clones in an unpublished study by a cloning company died within 48 hours of birth,[146] raising further concern about mortality rates in neonatal pig clones.

Conclusion 4: Juvenile growth and health
"Swine clones grew more slowly and weighed less at slaughter than sexually-derived comparators, although this difference may have been the result of immune challenge when clones were transitioned from a biosecure environment to a more conventional rearing facility (Viagen 2005)."

As with the study mentioned in the conclusion above, it appears that the FDA is searching for ways to raise uncertainty in order to dismiss troubling findings. The Viagen clones were small at birth, so it would not be unreasonable to think that cloning contributed to their small size at slaughter as well. In addition, there is evidence that the pig clones were abnormal in other ways. For example, "organ weights as a percentage of body weights were lighter for clones than for comparators,"[147] and some clones were clearly unhealthy (see below). While it is not completely certain what caused these problems, the fact that they occurred in one of the only studies of pig clones of this age should make the FDA more cautious about asserting the healthiness of these animals.

In fact, any conclusion made about the health of juvenile pig clones must be tempered by the fact that, other than the unpublished data set by Viagen, a cloning company with a vital interest in the outcome of the FDA risk assessment, there is only one peer-reviewed study on the health of pig clones of this age.

In this study (Archer et al. 2003a), data on the physiology, body weight, and clinical chemistry of five clones from one litter and four clones from another litter (both of the same cell line) were gathered at 15 and 27 weeks and compared to conventionally derived pigs.[148] Of these nine clones, one was perpetually small; one had abnormal teat distribution; one exhibited unusual hair growth pattern; and one displayed signs of hyperkeratosis, a condition which is indicative of a nutritional imbalance or gastrointestinal disorder and is known to result in reduced growth and appetite, diarrhea, and vomiting when severe.[149] Thus, four of nine clones exhibited some abnormality.

The FDA's conclusions about the health of juvenile pig clones should take into account that data on these animals is highly limited, involving only a small number of animals for just a few different cell lines, and that both of the studies reporting on the health of these animals found abnormalities and health problems.

Conclusion 5: Health of Viagen clones
"Three clones in the Viagen study were described as "poor doers," with periodic or chronic scouring and other health problems that resulted in poor growth. One clone was diagnosed with a lung adhesion at slaughter."

The FDA should also report that the clones in the Viagen study suffered from health problems that were significantly more likely to result in death relative to comparator pigs.[150] Three of the seven Viagen clones (43 percent) had to be euthanized before reaching slaughter age, compared to one of 16 comparators (six percent).

Also noted in the Viagen study was that swine clones had lower IGF-1 and estradiol-17ß levels at slaughter relative to the conventionally bred comparators, the significance of which the FDA should consider. In addition, blood values were variable among animals, making it difficult to identify any consistent trend or make any definitive conclusions about the underlying health of these animals one way or another. However, 11 percent (34/315) of clones' hematology measurements, and 24

percent (79/315) of clones' clinical chemistry measurements taken over five months were outside of the range of the comparator population.

Given that so little data are available on swine clones it should be concerning to the FDA that differences and problems have appeared in clones for many of the parameters observed, and that healthiness has not emerged as the overwhelming picture.

Conclusion 6: Reproductive health
"Reports from Martin (2004) and Viagen, Inc. (Appendix H) indicate normal fertility in boar and gilt clones."

These reports are the only two studies evaluating reproductive performance of swine clones, and there are flaws in the experimental design of both, particularly the Viagen study, that make it difficult to conclude anything about the reproductive health of clones.

The Martin et al. (2004) study, for example, involved only five female pig clones, four of whom were transgenic,[151] which the FDA has stated confounds the interpretation of results because it cannot be determined if the results obtained are due to the animal's clone status or transgenic status.[152] Thus, the reproductive performance of only one non-transgenic female pig clone was evaluated. This animal, moreover, was given additional opportunities to become pregnant compared to the non-clone gilts, which the authors stated could have influenced her reproductive performance.[153] Similarly, only one male pig clone was evaluated in this study. It is scientifically unsound for the FDA to base conclusions about an entire population of animals on a sample size of one.

The Viagen study reports data on just four male pig clones from only two different cell lines.[154] In addition, values for the clones are compared to just three control animals, one of whom was considered to be relatively old for a breeding boar. Thus, only two appropriate control animals were used to establish measures of 'normal' reproductive performance, an experimental design which is totally lacking in scientific rigor. With just four male clones and two comparator animals, it is impossible to make a statement about the reproductive health of boar clones with any confidence.

Conclusion 7: Post-pubertal maturation and aging
"No reports on post-pubertal maturation and aging of swine clones are currently available."

This statement is true and requires no further modification.

Conclusion 8: Progeny
"*Available reports from the literature and the Viagen Inc. dataset suggest that progeny of swine clones are not different from pigs derived through conventional breeding. The few reports of health problems in progeny of swine clones indicate they are not different either in quality or frequency from conventionally bred swine."*

The FDA should clarify its statement to reflect the fact that only two peer-reviewed studies and the Viagen data set report data on the health of progeny of swine clones. In addition, while one of the studies (Mir et al. 2005) bred nine female pig clones to one non-clone male, the authors reported

data on only 14 of the resulting progeny at 15 weeks of age, and eight progeny at 27 weeks of age.[155] No information is given on why or how that small subset of animals was chosen.

The Viagen study, moreover, found that the progeny of pig clones were more likely to die of "weakness" or "unknown causes" than comparator progeny.[156] The FDA dismisses this finding, however, because the problems were not seen consistently across litters, and because an episode of heat stress likely contributed to the loss of these animals. In actuality, cloning problems rarely manifest in a consistent manner, and 315 of the 688 pigs were exposed to high heat conditions. The fact that only the clone progeny suffered fatal problems is a finding that raises concern about the ability of these animals to withstand stress and maintain health.

In addition, 295 of 402 clone progeny (73.4 percent) reached slaughter age, whereas 243 of 300 (81 percent) of non-clone progeny survived to slaughter.[157] The FDA claims that the loss of an entire litter of clone progeny accounts for this difference, and that if this litter were removed from the data, survival rates for clone progeny and comparators would be similar. However, assuming an average litter size of 10, then removal of that clone progeny litter would increase the survival rate of clone progeny only negligibly (295 of 392 surviving, or 75 percent). Not only is this rate lower than that for the non-clone progeny in the Viagen study, it is substantially lower than national averages. According to the FDA, 11 percent of pigs die prior to weaning,[158] and an additional 0.9 percent of weaned pigs die,[159] making the overall national average survival rate 88 percent, far greater than the 75 percent predicted for the Viagen data set.

When so little data are available, the FDA should consider the significance of these concerning findings and exercise caution when making statements about the health of swine clone progeny, rather than asserting the normalcy of these animals with a confidence that is unfounded.

Interestingly, the FDA comments on both the quality *and frequency* of health problems in the progeny of swine clones. To be consistent, the FDA should comment on the frequency of health problems observed for all other clones of all other developmental nodes as well, which the FDA currently fails to do.

3.C Goat Health Risks

Very few studies have been performed on a very small number of goat clones. As a result, it is unclear if the lack of abnormalities reported in some studies indicates that cloned goats are healthy, or if problems could not be detected because of faults in experimental design, or if problems could not be detected because not enough animals have been studied. In addition, not all studies have indicated that cloned goats are 100 percent normal, and in fact, few cloning attempts in goats result in a live birth. Therefore, the FDA should exercise more caution when asserting that goat clones have not been reported to exhibit any health problems, as this creates the misleading impression that there is a large body of scientific evidence demonstrating that goat clones are healthy. In actuality, too little is known to make any reliable estimates of risks for cloned goats.

Analysis of FDA's conclusions[160]

Conclusion 1: Available information
"Although few studies have been performed on goat clones, some data is available for four of the five developmental nodes, and some limited information on progeny is also available."

Only six studies exist on the health of goat clones, and only some of these provide data for any given developmental node, and just three involve no or only some transgenic clones. Given that the FDA has stated that transgenic status confounds the interpretation of cloning study results,[161] there are effectively only three studies on goat clones, and none of these involve very large numbers of animals. In fact, the FDA reports a total of 31 live-born goat clones, of which no more than 16 are non-transgenic.[162]

The FDA acknowledges during its data analysis that it cannot be determined if the lack of complications reported in some studies is "the result of differences in methodology, species-specific differences, or simply an artifact of the small numbers of animals involved and small number of published papers."[163] The FDA should qualify *all* of its further remarks and conclusions about the health of goat clones with such a statement.

Conclusion 2: Large Offspring Syndrome
"Unlike cattle and sheep, goat clones do not appear to develop LOS."

There have been no reports of LOS, but very few studies have been published on goat clones, making it difficult to determine whether goat clones really do not develop LOS, or whether too few animals have been studied for LOS to have been detected.

In general, when discussing the health of goat clones, the FDA should report not just findings that suggest the clones are normal, but also findings that suggest potential causes for concern. Keefer et al. (2002), for example, reported the deaths of two goat clones during delivery (causes unspecified), which raises doubt that neonatal goat clones are normal and healthy.[164]

Conclusion 3: Pregnancy risks
"Likewise, there have been no adverse reports of pregnancy in surrogate goat does (i.e., hydrops and dystocia)."

There are only three reports on goats bearing clone pregnancies, only one of which involves non-transgenic goats, and no data regarding the effects of a clone pregnancy on labor and delivery for the surrogate dam. The lack of adverse reports, therefore, does not necessarily indicate that no problems occur, as so few animals were even studied.

In addition, Keefer et al. (2002) reports (though the FDA does not) that the nine goat clone births resulted from the transfer of a total of 145 clone embryos (6.2 percent overall success rate).[165] Of the 14 recipients of the clone embryos, only five were confirmed pregnant (35.7 percent), though all pregnancies were carried to term. Such low pregnancy and success rates are clearly of concern and should not be ignored by the FDA, as the tremendous inefficiency of the technology exposes numerous goats to the risks of cloning procedures.

Conclusion 4: Neonatal health
"Although three goat clones were reported to develop respiratory problems, it could not be determined from the study (Keefer et al. 2001a) whether this was related to cloning or not."

It should be noted that respiratory problems were due to bacterial infection and were fatal.

The FDA should also mention that there is some indication in the published literature that blood values may be different between goat clones and comparators. Behboodi et al. (2005), for example, found that for a group of seven transgenic clones (who have limited relevance to non-transgenic clones), six of 24 clinical chemistry values were significantly different than normal, and one of 19 was outside the published range.[166] There is not enough information known from the study to thoroughly evaluate the significance of these differences, but the finding should signal that there are potential concerns with the health status of goat clones.

Conclusion 5: Growth, maturity, and progeny
"Goats appear to grow and mature normally and produce normal progeny."

With only two studies reporting on the reproductive performance of goat clones, one involving just three males,[167] and the other involving five transgenic females,[168] and neither providing very many details, there is insufficient data to make any compelling conclusions about the reproductive health of these animals.

Conclusion 6: Shortened telomeres
"The potential effect of shortened telomeres in one report on progeny of goat clones cannot be estimated at this time."

This statement requires no further modification. In fact, it should serve as a model for the rest of the FDA's conclusions about cloned goats: The potential effect of cloning on the health and reproductive performance of goat clones and their progeny cannot be estimated at this time.

Conclusion 7: Post-pubertal maturation
"No data on post-pubertal maturation are available for goats at this time."

This statement requires no further modification.

3.D Sheep Health Risks

In general, we agree with the FDA's conclusions about health risks for cloned sheep, as too little information is available to make any reasonable assertions about the health of these animals, and what evidence exists suggests major health problems and abnormalities in cloned sheep. However, the FDA should more accurately portray the serious risks that sheep clones have so far been reported to face. In addition, given the similarity in severe health problems observed in sheep clones to the problems consistently documented in cow clone studies, we would suggest that the FDA exercise similar caution in regulating cow cloning.

Analysis of FDA's Conclusions[169]

Conclusion 1: Overall conclusions on sheep clones
Data on sheep SCNT clones is scarce and, except for anecdotal reports, do not extend beyond the perinatal period. Existing data for Developmental Nodes I and II suggest that surrogate ewes and neonatal lamb clones experience similar problems as cattle clones and their surrogates (hydrops, dystocia, LOS). However, given the very few studies that have been conducted and the few animals involved, it cannot be determined whether the frequency of these abnormalities are elevated compared to other ART in sheep. One study (Ptak et al. 2002) indicated that the incidence of LOS in lamb clones was not different from IVP lambs, although actual numbers of lambs with LOS for each ART method was not reported in this study. Data for Developmental Nodes III and IV and progeny are only available for BNT clones, and only from one study. The only information available for Developmental Node V is from the death of Dolly and another sheep clone of unknown age."

The FDA is accurate in stating that essentially no information is available on sheep clones, and thus no conclusions can be made asserting the health and normalcy of these animals. In fact, not much more information is available on goat clones either (see above), which suggests that the FDA should be withholding judgment on goat clones as well.

In addition, the available information on sheep clones suggests that these animals suffer similar risks of health problems as cow clones, including high rates of pregnancy loss, fetal abnormalities, still births, and neonatal death,[170] in addition to the hydrops, dystocia, and LOS mentioned by the FDA, which suggests that the FDA should be similarly concerned about cow clones as well. It is also interesting that the FDA discusses the frequency of abnormalities in sheep clones, but fails to do so for cow clones. To be consistent, the FDA should engage in this level of analysis for all cloned animals.

In the interest of completeness, the FDA should also report the overall mortality rate for sheep clones. According to the two studies cited by the FDA,[171] 14 of 18 live-born clones (77.8 percent) did not survive to the juvenile period, compared to only two percent of conventionally bred sheep in the U.S. While this is only preliminary data, the huge difference between sheep clones and conventional sheep indicates that sheep clones face significant risks.

3.E General Conclusions

Analysis of FDA's conclusions[172]

The FDA's summaries of the animal health risks associated with cloning that appear at the end of the "Animal Health Risks" chapter, and also in the "Executive Summary" and "Summary and Conclusions" chapters, suffer from many of the same problems already noted.

For example, the FDA repeatedly asserts that cloned animals surviving the perinatal period are normal and healthy, display normal reproductive function, and produce normal and healthy progeny.[173] The FDA further states at the end of the Summary and Conclusions chapter that "all" problems resolve as the surviving cloned animals mature, and that adult clones are normal in "all of the measures that have been thus far investigated."[174]

However, these assertions are clearly overstated and unfounded by the data, as there is too little information concerning these topics, particularly for swine, goats, and sheep, to conclude anything with certainty. In addition, whatever little data exist contain several findings that suggest that older clones and progeny may indeed exhibit abnormalities and health problems. Furthermore, cloning researchers have recognized that it may be impossible for any clone to ever be considered normal, as even those clones who appear healthy may have subtle genetic abnormalities that do not result in an obvious phenotype.[175,176,177]

The FDA should note the insufficiency of the data concerning health risks in clones past the perinatal period, and the uncertainty that necessarily results. The FDA does this appropriately at the end of the Animal Health Risks chapter,[178] but fails to do so otherwise. In addition, the FDA should report not just findings indicating that clones are healthy, but also those findings that raise doubt and concern about the health of clones. In this way, the FDA can avoid creating the misleading impression that there is a solid scientific basis for asserting the normalcy of cloned animals, which there is not.

In addition, for neonatal clones and their surrogate mothers, the FDA needs to strengthen its statements about the risks these animals face to more accurately reflect the severity consistently demonstrated in the scientific literature. Currently, the FDA qualifies many of its statements by saying that "some" animals are "possibly" at risk or "appear" to be at risk, as in the following statement from the Executive Summary: "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."[179] However, there is overwhelming evidence that serious, typically fatal, health problems and abnormalities are repeatedly and frequently seen in many neonatal clones and surrogates carrying clone pregnancies.

Another particularly egregious example of how the FDA downplays cloning related risks is the statement that "the frequency of live normal births appears to be low."[180] In fact, virtually *every* cloning study to date reports that *less than 10 percent* of clone pregnancies result in a live normal birth, and less than five percent of cloning attempts succeed in producing a live, relatively healthy animal. The FDA should report figures such as these concerning the overall morality rate seen in cloning

studies, which it fails to do at any point in the risk assessment, and form more representative conclusions that do not downplay and distort the true nature of cloning risks.

An example of a more appropriate statement regarding the risks associated with cloning is provided in the Summary and Conclusions chapter, where the FDA states that "significant adverse outcomes have been reported for animal clones and their dams," resulting in "high gestational mortality."[181] The FDA goes on to acknowledge that post-natal mortality "is higher in clones than in animals produced using other assisted reproductive technologies (ARTs)." These are the strongest statements the FDA makes in the entire risk assessment, and are far more representative of the true nature of cloning risks than the FDA's other statements.

However, the FDA then qualifies this statement by claiming that the situation appears to be improving as the technology matures,[182] which is entirely unsupported by the scientific literature. In fact, leading MIT cloning researcher Rudolf Jaenisch has been quoted as saying, "There's been zero progress. I mean it. Zero. The only thing we've begun to realize is how big the problem is…,"[183] and another cloning researcher, Peter Mombaerts of Rockefeller University, has stated that his best hopes for an "extremely efficient" version of cloning would have only a 20-30 percent success rate.[184]

Future efficiency rates for cloning are purely speculative, and the FDA's conclusions about cloning risks, particularly as such conclusions inform the FDA's decision on how to regulate cloned animals currently, should not be based on a hypothetical state of the technology that may or may not occur. The FDA must regulate cloning based on how it currently works, which is extremely inefficiently.

Lastly, and very importantly, the FDA needs to place less of an emphasis on the qualitative similarity of the problems seen in cloned animals compared to animals produced using ARTs, and greater emphasis on the quantitative differences.[185] In the agency's general concluding remarks, the FDA repeatedly highlights that the problems observed in clones are not unique and have been seen in animals produced through more conventional means.[186]

However, the FDA fails to mention that the problems are seen in clones at a significantly higher rate, so much so that it raises new concerns about the well being of these animals. A problem (e.g., hydrops) that occurs in 28 percent of cloned animals, but in just one of 7,500 conventional cattle, cannot reasonably be argued to be similar in nature.[187] In fact, if risk equals the likelihood of adverse outcome given exposure, as the FDA states,[188] then because cloning significantly increases the likelihood of adverse outcomes, the FDA should find that cloning does indeed present unique risks that are not seen with ARTs.

By repeatedly dismissing cloning risks as being 'nothing new,' the FDA is creating the misleading impression that there is nothing concerning about the problems seen in cloning. The FDA needs to be more fair and honest in how it characterizes the risks that the animals involved in the cloning process face.

4. Risk Management Plan

According to the FDA and the National Academy of Sciences, "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."[189] As such, the FDA's risk management plan is based on the same faulty conclusions crafted in the agency's risk assessment and needs to be entirely revised to adequately address the serious threats to animal health that are associated with the cloning process. The FDA's plan should, in fact, call for a ban on animal cloning as the only way to protect animal health.

The FDA states that maximizing safety is a goal of risk assessors, and defines safety as "the condition under which risks would be considered unlikely…."[190] The FDA also states that a component of the risk management process is "identifying and evaluating alternative strategies (often regulatory) to deal with the risks characterized in the risk assessment."[191] Yet the FDA offers just one risk management option: no regulation. No regulation of cloning, however, will not making cloning risks unlikely, and is entirely insufficient to promote the safety of the animals involved in the cloning process.

Furthermore, the FDA's only proposal for minimizing the impact of cloning risks is to "encourage the development of standards of care for animals involved in the cloning process…."[192] However, this will do little to mitigate cloning risks, as the majority of cloned animals are already produced in settings with elaborate veterinary care, and nearly all cloning attempts still fail, with animals suffering serious health problems and dying prematurely. In fact, according to a study done by Cyagra, a major cloning company, 42 percent of neonatal calves died within 150 days of birth, despite being monitored extensively and receiving substantial veterinary care and intervention.[193,194,195]

The FDA must therefore consider other plans and evaluate alternative regulatory options to address the serious and frequent risks involved with cloning, including a ban on animal cloning. The determination of which plan to adopt, moreover, must necessarily involve the consideration of "social, economic, ethical, and political conditions or criteria,"[196,197] which would include the consideration of animal welfare.[198]

Consequently, given the nature and extent of risks that cloned animals face, and given that scientists consider these risks to "create serious animal welfare concerns that limit the acceptability and utility of the present technology,"[199] the FDA should recommend a mandatory ban on the use of products from cloned animals and their progeny in the human and animal feed supply as the only legitimate option for protecting animals from cloning risks.

Furthermore, consideration of other ethical, social, economic, and political factors does not offer any justification for approving cloning at the expense of animal welfare. The value of cloning, even as characterized by the FDA,[200] is minor.[201]

In fact, numerous statements have been made by the food industry that criticize the usefulness of cloning. The International Dairy Foods Association, for example, has stated that "there currently is no consumer benefit in milk from cloned cows."[202]

Furthermore, the vast majority of the American public has repeatedly demonstrated that it does not want animals to be cloned for food. In poll after poll, approximately two thirds of American consumers say they do not approve of animal cloning,[203] and a recent poll indicated that that number increases to 88 percent when respondents are informed that cloning involves animal suffering.[204] A poll by the International Food Information Council found that 58 percent of respondents would be unlikely to buy products from cloned animals or their progeny even if the FDA determined they were safe to eat.[205]

Given the tremendous increasing in animal suffering caused by cloning, as supported by the scientific literature, and the fact that neither the American public nor the food industry is clamoring for cloned foods, the FDA must consider that approval is not the appropriate regulatory option for animal cloning. Instead, a mandatory ban on animal cloning is the only acceptable option for the FDA to recommend.[206]

5. Conclusion

The FDA's conclusions about the animal health risks associated with cloning are premature and unsupported by the scientific literature. The agency's risk management plan, moreover, is not an adequate response to the serious nature of the risks faced by the vast majority of animals involved in the cloning process.

There are little data – only a handful of studies analyzing limited numbers of animals – on the health of cloned pigs, goats, or sheep; the health of older cloned cows; or the health of clone progeny. Much of the data that do exist are subject to publication bias since the studies are conducted by commercial cloning companies who are more likely to report positive findings because they have a vested interest in the outcome of the FDA's decision-making process.

Too little is known about cloning, and what is known demonstrates clearly that cloning has a tremendous impact on animal life. Given that there is little potential benefit from cloning, that neither consumers nor the food industry are interested in cloning, and that cloning jeopardizes animal welfare, the FDA should not approve animal cloning in food production. Instead, AAVS recommends that the FDA address the issues raised in these comments and protect animal health by imposing a ban on the use of cloned animals and their progeny in the human food and animal feed supply.

6. Endnotes

[1] Food and Drug Administration (2006). Animal Cloning: A Draft Risk Assessment. December 28, 2006. (Hereinafter referred to as "FDA RA.") P. 8-9, 14, 306.
[2] These comments specifically address the animal health risks associated with cloning and do not examine the food safety issues. However, as with the animal health sections of the risk assessment, AAVS believes that the FDA also fails to adequately address the safety of cloned food products in the human food and animal feed supply.
[3] FDA RA, P. 41.
[4] FDA RA, P. 41.
[5] FDA RA, P. 4.
[6] FDA RA, Appendix A, P. A-6.
[7] FDA RA, P. 41.
[8] FDA RA, P. 5.
[9] National Academy of Sciences/National Research Council (2002). *Animal Biotechnology: Science-Based Concerns*. National Academies Press: Washington, D.C. P. 33.
[10] Codex Alimentarius Commission (2004). *The Joint FAO/WHO Food Standards Programme Procedural Manual*, *14th Edition*. P.46.
[11] FDA RA, P. 43-44.
[12] e.g., FDA RA, P. 8.
[13] Based on assessment of data and studies presented in FDA RA.
[14] e.g., FDA RA, P. 14.
[15] e.g., FDA RA, P. 104-106.
[16] e.g., Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.
[17] FDA RA, P. 10.
[18] It is questionable whether ARTs are even the appropriate comparators for cloning. Given that problems do occur with ARTs, particularly with more recent ARTs such as *in vitro* fertilization and BNT, they serve as a dubious benchmark for measuring animal health. Cloning, in any case, is not even an assisted reproductive technology, as no reproductive event ever occurs.
In addition, it would be more informative for the FDA to compare cloning to natural breeding. Statistically speaking, while ARTs may not be significantly different than natural breeding, and cloning may not be significantly different than ARTs, cloning may be significantly different than natural breeding. It turns out that this point is somewhat moot, as cloning is significantly worse than ARTs. However, a comparison between cloning and natural breeding would still be useful in determining the full impact of cloning on animal health, especially since many animals are reproduced naturally.
[19] e.g., Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.
[20] National Research Council (2007). *Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget*. National Academies Press: Washington D.C. P. 197.
[21] National Academy of Sciences/National Research Council (1983). *The Red Book: Risk Assessment in the Federal Government: Managing the Process*. National Academy Press: Washington D.C. P. 18-19. Further elaborated in National Academy of Sciences/National Research Council (1996).

Understanding Risk: Informing Decisions in a Democratic Society. National Academies Press: Washington D.C.

[22] The Codex Alimentarius Commission also states that risk management must involve the "weighing of policy alternatives, in consultation with all interested parties," a process in which the FDA does not engage. Given that cloning raises obvious concerns about animal welfare, ethics, and consumer choice, numerous parties have a stake that has not been considered in the FDA's decision. A moratorium on the use of animal cloning must be maintained until these parties can be included in the process and their concerns can be addressed.

[23] Conclusions stated in FDA RA, P. 152-153.

[24] Wells, D.N., Misica, P.M., & Tervit, H.R. (1999). Production of cloned calves following nuclear transfer with cultured adult mural granulose cells. *Biology of Reproduction, 60*, 996-1005.

[25] Heyman, Y., Chavatte-Palmer, P., LeBourhis, D., et al. (2002). Frequency and occurrence of late-gestation losses from cattle cloned embryos. *Biology of Reproduction, 66*, 6-13.

[26] Wells, D.N., Forsyth, J.T., McMillan, V., & Oback, B. (2004). The health of somatic cell cloned cattle and their offspring. *Cloning and Stem Cells, 6*(2), 101-110.

[27] Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.

[28] FDA RA, P. 107

[29] Lawrence, J.L., Schrick, F.N., Hopkins, F.M., et al. (2005). Fetal losses and pathologic findings of clones derived from serum-starved versus serum-fed bovine ovarian granulosa cells. *Reproductive Biology, 5*(2), 171-184.

[30] Lee, R.S.F., Peterson, J.A., Donnison, M.J., et al. (2004). Cloned cattle fetuses with the same nuclear genetics are more variable than contemporary half-siblings resulting from artificial insemination and exhibit fetal and placental growth deregulation even in the first trimester. *Biology or Reproduction, 70*, 1-11.

[31] FDA RA, P. 107.

[32] FDA RA, P. 108.

[33] Chavatte-Palmer, P., Remy,D., Cordonnier, N., et al. (2004). Health status of cloned cattle at different ages. *Cloning and Stem Cells, 6*(2), 94-100.

[34] FDA RA, P. 108.

[35] Batchelder, C.A. (2005). Cloning in Cattle: Effect of the Nuclear-Donor Cell on Cloning Efficiency, Perinatal Physiology, and Long-term Health of Cloned Calves.

[36] Wells, D.N., Misica, P.M., & Tervit, H.R. (1999). Production of cloned calves following nuclear transfer with cultured adult mural granulose cells. *Biology of Reproduction, 60*, 996-1005.

[37] FDA RA, P. 116.

[38] FDA RA, P. 95.

[39] FDA RA, P. 112.

[40] FDA RA, P. 112.

[41] FDA RA, P. 111.

[42] FDA RA, P. 113.

[43] FDA RA, P. 111.

[44] FDA RA, P. 112.

[45] FDA RA, P. 111.

[46] FDA RA, P. 114.

[47] FDA RA, P. 116-117.
[48] FDA RA, P. 115.
[49] Kruip, Th.A.M., & den Daas, J.H.G. (1997). In vitro produced and cloned embryos: Effects on pregnancy, parturition and offspring. *Theriogenology, 47*, 43-52.
[50] FDA RA, P. 8.
[51] FDA RA, P. 118, 122-123.
[52] FDA RA, P. 123.
[53] FDA RA, P. 124.
[54] FDA RA, P. 117.
[55] FDA RA, P. 119-120.
[56] FDA RA, P. 124.
[57] FDA RA, P. 120.
[58] FDA RA, P. 119-120.
[59] FDA RA, P. 119-120.
[60] FDA RA, P. 115.
[61] FDA RA, Table V-4, P.119-120.
[62] FDA RA, P. 14.
[63] Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.
[64] FDA RA, P. 35.
[65] FDA RA, Table V-1, P. 104-106.
[66] FDA RA, P. 121.
[67] FDA RA, P. 116.
[68] FDA RA, P. 117.
[69] FDA RA, Appendix A, P. A-6.
[70] FDA RA, P. 124.
[71] FDA RA, P. 117.
[72] FDA RA, Table V-1, P. 104-106.
[73] FDA RA, P. 10.
[74] FDA RA, P. 14.
[75] FDA RA, P. 117.
[76] FDA RA, P. 121.
[77] FDA RA, P. 9.
[78] See, for example, reports from Wells et al. 2004, Cyagra 2003, Batchelder 2005, and Chavatte-Palmer et al. 2004, summarized in FDA RA, P.127-133.
[79] FDA RA, P. 133-134.
[80] FDA RA, P. 127.
[81] FDA RA, Appendix E.
[82] Rudenko, L. & Matheson, J.C. (2007) The US FDA and animal cloning: Risk and regulatory approach. *Theriogenology*. 198-206.
[83] Lawrence, J.L., Schrick, F.N., Hopkins, F.M., et al. (2005). Fetal losses and pathologic findings of clones derived from durum-starved versus serum-fed bovine ovarian granulosa cells. Reproductive Biology, 5(2), 171-184.

[84] FDA RA, P. 129.
[85] FDA RA, P. 133.
[86] FDA RA, P. 127.
[87] FDA RA, P. 130.
[88] FDA RA, P. 128.
[89] FDA RA, P. 134.
[90] FDA RA, P. 131.
[91] FDA RA, P. 127.
[92] FDA RA, P. 134.
[93] FDA RA, P. 135.
[94] FDA RA, P. 134.
[95] FDA RA, P. 140.
[96] Heyman, Y., Chavatte-Palmer, P., Berthelot, V., et al. (2007). Assessing the quality of products from cloned cattle: An integrative approach. *Theriogenology, 67*, 134-141.
[97] FDA RA, P. 141.
[98] FDA RA, P. 86.
[99] FDA RA, P. 142.
[100] FDA RA, P. 143.
[101] FDA RA, P. 144-145.
[102] FDA RA, P. 145.
[103] FDA RA, P. 145-146.
[104] FDA RA, P. 146.
[105] FDA RA, P. 144.
[106] FDA RA, P. 98.
[107] FDA RA, P. 11.
[108] FDA RA, P. 147.
[109] FDA RA, P. 99.
[110] FDA RA, P. 101.
[111] FDA RA, P. 104.
[112] FDA RA, P. 148.
[113] FDA RA, P. 148.
[114] FDA RA, P. 148.
[115] FDA RA, P. 148.
[116] In addition, there could be clinical relevance to values that are consistently different, falling within a different part of the range than comparators' values, even if all values fall within the published range. See, for example, Heyman et al. (2007).
Heyman, Y., Chavatte-Palmer, P., Berthelot, V., et al. (2007). Assessing the quality of products from cloned cattle: An integrative approach. *Theriogenology, 67*, 134-141.
[117] Ortegon, H., Betts, D.H., Lin, L., et al. (2007). Genomic stability and physiological assessments of live offspring sired by a bull clone, Starbuck II. *Theriogenology, 67*, 116-126.
[118] FDA RA, P. 120.
[119] FDA RA, P. 124.
[120] FDA RA, P. 121.

[121] FDA RA, Appendix E.
[122] FDA RA, P. 125-126.
[123] FDA RA, P. 130.
[124] FDA RA, P. 120.
[125] FDA RA, P. 129.
[126] FDA RA, P. 148.
[127] Lawrence, J.L., Schrick, F.N., Hopkins, F.M., et al. (2005). Fetal losses and pathologic findings of clones derived from starved-starved versus serum-fed bovine ovarian granulosa cells. *Reproductive Biology, 5*(2), 171-184.
[128] Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.
[129] Conclusions stated in FDA RA, P. 164.
[130] National Agriculture Statistics Service (2007). *Quarterly Hogs and Pigs*. Retrieved April 2007, from http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1086.
[131] FDA RA, P. 154.
[132] FDA RA, P. 154.
[133] FDA RA, P. 157-159.
[134] FDA RA, P. 154.
[135] Polejaeva, I.A., Chen, S-H., Vaught, T.D., et al. (2000). Cloned pigs produced by nuclear transfer from adult somatic cells. *Nature, 407*, 86-90.
[136] FDA RA, P. 154.
[137] FDA RA, P. 154.
[138] Betthauser, J., Forsberg, E., Augenstein, M., et al. (2000). Production of cloned pigs from in vitro systems. *Nature Biotechnology, 18*, 1055-1059.
[139] Onishi, A., Iwamoto, M., Akita, T., et al. (2000). Pig cloning by microinjection of fetal fibroblast nuclei. *Science, 289*, 1188-1190.
[140] Polejaeva, I.A., Chen, S-H., Vaught, T.D., et al. (2000). Cloned pigs produced by nuclear transfer from adult somatic cells. *Nature, 407*, 86-90.
[141] Martin, M., Adams, C., & Wiseman, B. (2004). Pre-weaning performance and health of pigs born to cloned (fetal cell derived) swine versus non-cloned swine. *Theriogenology, 62*, 113-122.
[142] FDA RA, P. 156.
[143] FDA RA, P. 156.
[144] FDA RA, P. 157.
[145] FDA RA, P. 156-157.
[146] FDA RA, P. 157.
[147] FDA RA, P. 161.
[148] FDA RA, P. 160.
[149] FDA RA, P. 161.
[150] FDA RA, Appendix F.
[151] FDA RA, P. 162.
[152] FDA RA, P. 5.
[153] Martin, M., Adams, C., & Wiseman, B. (2003). Pre-weaning performance and health of pigs born to cloned (fetal cell derived) swine versus non-cloned swine. *Theriogenology, 62*, 113-122.

[154] FDA RA, Appendix F.
[155] Mir, B., Zaunbrecher, G., Archer, G.S., et al. (2005). Progeny of somatic cell nuclear transfer (SCNT) pig clones are phenotypically similar to non-cloned pigs. *Cloning and Stem Cells, 7*(2), 119-125.
[156] FDA RA, Appendix F.
[157] FDA RA, Appendix F.
[158] FDA RA, P. 155.
[159] FDA RA, P. 160.
[160] Conclusions stated in FDA RA, P. 173.
[161] FDA RA, P. 5.
[162] FDA RA, P. 169.
[163] FDA RA, P. 170.
[164] FDA RA, P. 170.
[165] Keefer, C.L., Keyston, R., Lazaris, A., et al. (2002). Production of cloned goats after nuclear transfer using adult somatic cells. *Biology of Reproduction, 66* (199-203).
[166] FDA RA, P. 171.
[167] Gauthier et al. (2001), reported in FDA RA, P. 172.
[168] Reggio et al. (2001), reported in FDA RA, P. 172.
[169] Conclusions stated in FDA RA, P. 168-169.
[170] FDA RA, P. 165-168.
[171] FDA RA, P. 165.
[172] Conclusions stated in FDA RA, P. 175-176, as well as P. 3-15, 305-309.
[173] FDA RA, P. 9, 14, 175-176, 306, 309.
[174] FDA RA, P. 306.
[175] Jaenisch, R. (2004). Human cloning – The science and ethics of nuclear transplantation. *New England Journal of Medicine, 351*(27), 2787-2791.
[176] Humphreys, D., Eggan, K., Akutsu, H., et al. (2002). Abnormal gene expression in cloned mice derived from embryonic stem cell and cumulus cell nuclei. *Proceedings of the National Academy of Sciences, 99*(20), 12889-12894.
[177] Wells, D.N., Forsyth, J.T., McMillan, V., & Oback, B. (2004). The health of somatic cell cloned cattle and their offspring. *Cloning and Stem Cells, 6*(2), 101-110.
[178] FDA RA, 175-176.
[179] FDA RA, P. 4-5.
[180] FDA RA, P. 14, 309.
[181] FDA RA, P. 306.
[182] FDA RA, P. 306, repeated elsewhere.
[183] Meek, J. (2002, April 19). Tears of a clone. *The Guardian*. Retrieved December 6, 2006, from http://www.guardian.co.uk/genes/article/0,2763,686989,00.html.
[184] Gardner, A. (2007, February 12). Scientists clone mice from hair follicle stem cell. *Washington Post*. Retrieved February 12, 2007, from http://www.washingtonpost.com/wp-dyn/content/article/2007/02/12/AR2007021200987.html.
[185] The Codex Alimentarius Commission states, in fact, that risk assessment "should use available quantitative information to the greatest extent possible."
[186] FDA RA, P. 10, 14, 306, 309.

[187] In addition, the FDA should not suggest that it is the *in vitro* component of the cloning process that causes the problems seen in cloned animals, as many studies have found that health problems are increased in clones even compared to animals produced through *in vitro* fertilization. See, for example, Lee et al. (2004); Heyman et al. (2002); Chavatte-Palmer et al. (2002).
[188] FDA RA, P. 48.
[189] FDA RMP.
[190] FDA RA, Appendix A, P. A-6.
[191] FDA RMP.
[192] FDA RMP.
[193] Panarace, M., Aguero, J.I., Garrote, M., et al. (2007). How healthy are clones and their progeny: 5 years of field experience. *Theriogenology, 67*, 142-151.
[194] In addition, the FDA evaluates cloning risks with the assumption that cloned animals will primarily be used for breeding purposes and will not be used extensively for food production (FDA RA, P. 53-54). However, there is nothing in the risk management plan to ensure that this is so. Without restrictions on the use of animal cloning, the risk management plan is inadequate to address the scope of risks that may arise with different applications of cloning
[195] The FDA also states that "it is likely that genomics, proteomics and metabolomics will see increased use for such purposes [i.e., to survey animal health] in the future" (FDA RA, P. 49), yet offers no plan for how to incorporate data from such studies into its position on cloning. If animal cloning is allowed, the risk management plan needs to include provisions for post-approval monitoring and for how the FDA plans to reevaluate its recommendations on the basis of newly acquired information.
[196] FDA RA, P. 42.
[197] Also prescribed by: National Academy of Sciences/National Research Council (1983). *The Red Book: Risk Assessment in the Federal Government: Managing the Process*. National Academy Press: Washington D.C. P. 18-19;
and by National Academy of Sciences/National Research Council (1996). *Understanding Risk: Informing Decisions in a Democratic Society*. National Academies Press: Washington D.C.
[198] The Codex Alimentarius Commission, of which the U.S. is a member and which sets food standards for the international community, also states that risk management must involve the weighing of policy alternatives, and further calls for "consultation with all interested parties." The FDA thus must revise its risk management plan to not only comply with national guidelines, but also international guidelines governing risk analysis. The FDA must also incorporate issues raised by those parties with an interest in the outcome of the FDA's position, including those with concerns about animal welfare, ethics, and consumer choice.
[199] Wells, D.N., Forsyth, J.T., McMillan, V., & Oback, B. (2004). The health of somatic cell cloned cattle and their offspring. *Cloning and Stem Cells, 6*(2), 101-110.
[200] FDA RA, P. 4.
[201] Cloning, if it works, only allows the reproductive capabilities of an animal to be doubled. A cloned animal must still be bred, and the normal unpredictability of fertilization and sexual reproduction must still occur. In addition, a high degree of variability is seen in clones. Archer et al. (2003), for example, found that cloning increased variability for certain traits, and data from the Cyagra data set demonstrated that "clones from the same cell line showed considerable variation in their phenotype" (FDA RA, Appendix E). The Cyagra data also raised the question as to whether

conformation of an animal, an important characteristic for breeding programs, "is a function of its uterine environment or changes in gene expression" (FDA RA, Appendix E). Such findings again cast doubt on the utility of cloning to "allow for the propagation of known genotypes and phenotypes without the risk of genetic reshuffling" (FDA RA, P.4).
Archer, G.S., Dindot, S., Friend, T.H., et al. (2003). Hierarchical phenotypic and epigenetic variation in cloned swine. *Biology of Reproduction, 69*, 430-436.

[202] Statement of International Dairy Foods Association, RE: FDA's draft risk assessment on milk and meat from cloned animals. Released December 28, 2006. Accessed from http://www.idfa.org/reg/cloning_idfa_statement_12-28-06.pdf

[203] See, for example, Pew Initiative on Food and Biotechnology (2006). Public Sentiment About Genetically Modified Food, December 2006 Update. Retrieved from http://pewagbiotech.org/research/2006update/.
See also, *Animal Cloning and the Production of Food Products: Perspectives from the Food Chain* (2002). P. 23.

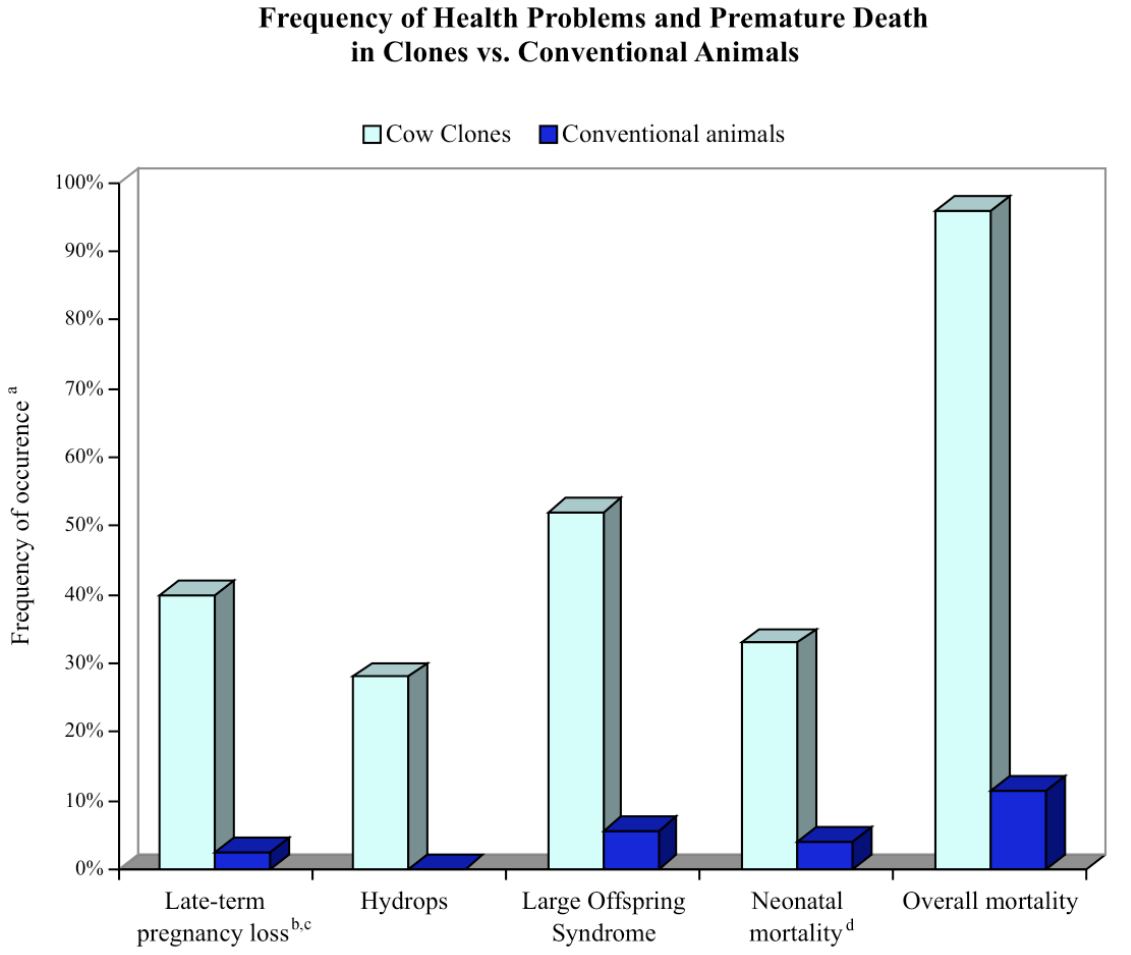
[204] AAVS News Release (2006, December 28). FDA gives green light to cloning animals for food despite new survey indicating overwhelming public concern.

[205] IFIC (2006). Food Biotechnology: A study of U.S. consumer attitudinal trends. Retrieved from http://ific.org/research/biotechres.cfm

[206] Though the FDA may consider some of these ethical and social considerations to be outside its purview, the agency recognizes that "all relevant issues need to be considered" (FDA RMP) in the development of a risk management plan. Therefore, until such time as these matters can be discussed in more appropriate fora to develop a comprehensive risk management plan, the FDA must nevertheless maintain a ban on the cloning of animals for food. The scientific literature supports such a stance, and to do otherwise would be to make a decision without allowing all issues of relevance the full consideration they are owed.

Figure 1. Frequency of Adverse Outcomes in Cows

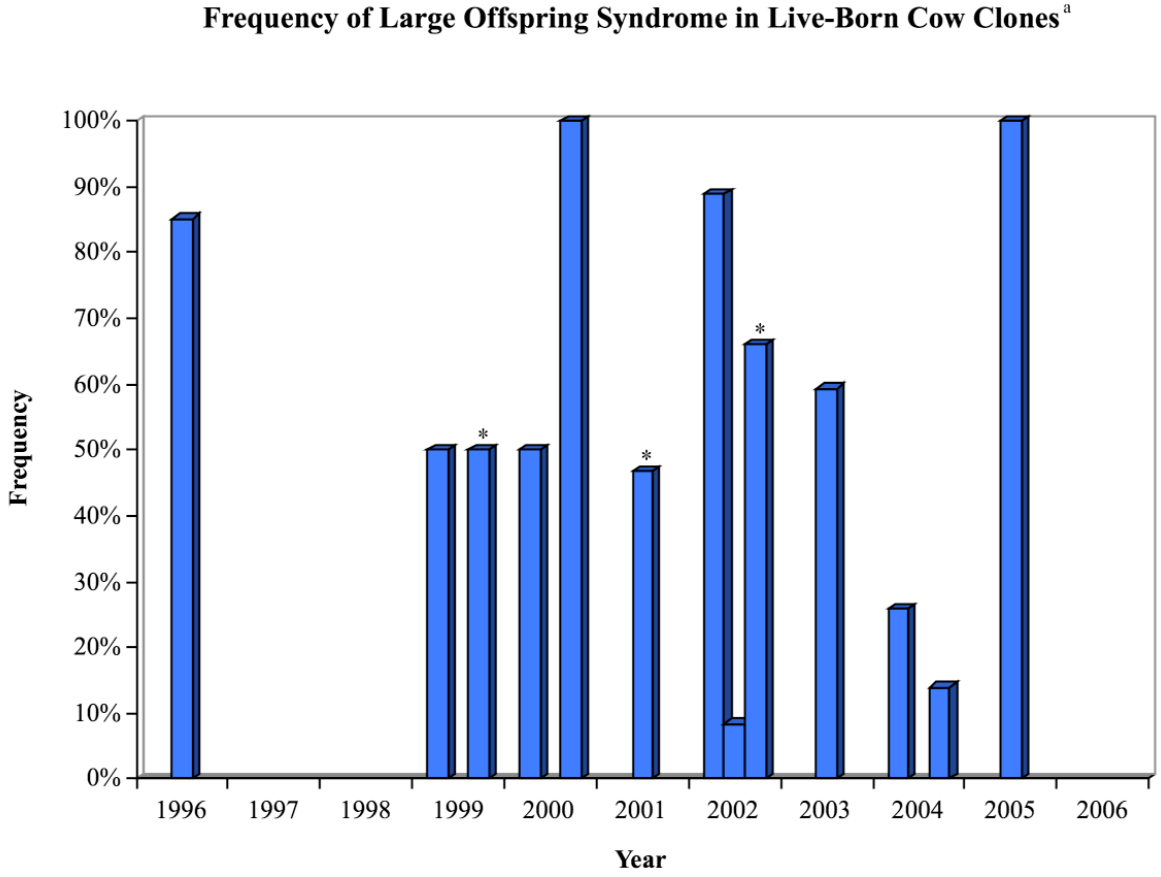
A comparison of the occurrence of adverse outcomes in cloned cows and conventionally bred cows demonstrates that clones are tremendously more likely to suffer serious health problems and die prematurely.



[a] Percentages are approximate and based on data provided in the FDA Risk Assessment, except where otherwise noted.
[b] Expressed as a percentage of pregnancies confirmed at Day 90 of gestation.
[c] Based on data from the FDA RA, Panarace et al. (2007), Lawrence et al. (2005), Heyman et al. (2002), and Wells et al. (1999).
[d] Expressed as a percentage of live-born calves.

Figure 2. Frequency of Large Offspring Syndrome Over Time

Reviewing the incidence of Large Offspring Syndrome reported in studies from 1996-2006 demonstrates that LOS incidence has remained consistently high and is not decreasing with time, contrary to the FDA's position.

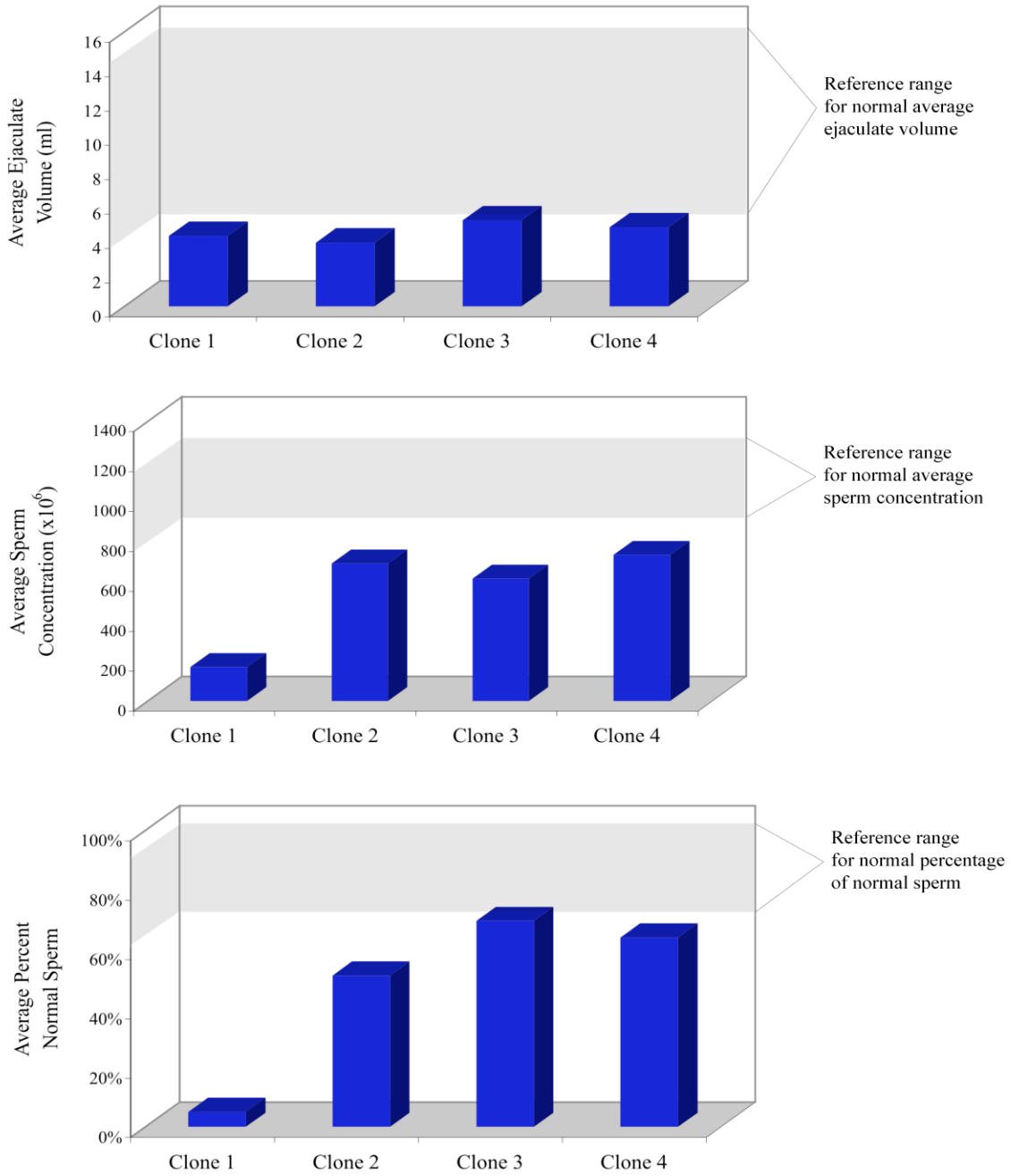


[a] Based on data provided in the FDA Risk Assessment (P. 119-120)
* Study involves at least some transgenic clones

Figure 3. Evaluation of Reproductive Health of Four Bull Clones

An evaluation of the semen collected from four bull clones demonstrates that the clones' values were all below normal ranges or on the low end of normal, contradicting the FDA's analysis that these clones have normal reproductive function.

Semen Evaluation of Four Bull Clones Compared to Reference Ranges [a]



[a] Based on data provided in the FDA Risk Assessment (P. 147)