Not Ready for Prime Time:

FDA's Flawed Approach to Assessing the Safety of Food from Animal Clones

Executive Summary

In December 2006, the Food and Drug Administration (FDA) announced it had completed its "risk assessment"[i] on food from animal clones. Our report, "Not Ready for Prime Time: FDA's Flawed Approach to Assessing the Safety of Food from Animal Clones" analyzes FDA's risk assessment and its conclusion (stated in the Agency's press release) that FDA "finds that meat and milk from clones of adult cattle, pigs and goats, and their offspring, are as safe to eat as food from conventionally bred animals."[ii]

Our analysis finds that FDA's conclusion of safety is based upon scant data from few peer-reviewed studies. Furthermore, the Agency's assessment of the data is slanted, information is selectively reported to fit predetermined conclusions, and FDA fails to consider possible side-effects of cloning that independent scientists, including the National Academy of Sciences (NAS), say should be considered in a regulatory review. Also troubling is our finding that FDA's assessment relies heavily on unpublished data from two cloning companies who have a financial interest in FDA approval,[iii] and on studies that make use of this same data.

Our review of FDA's risk assessment finds that for direct studies of meat or milk, the agency based its "safety" finding on the following:

- FDA found no peer-reviewed studies on meat from cloned cattle or on milk or meat from the offspring of cow clones.
- FDA found no peer-reviewed studies on meat from cloned pigs or their offspring.
- FDA found no peer-reviewed studies on meat or milk from cloned goats or their offspring.
- FDA found just three peer-reviewed studies on milk from cloned cows; all three studies showed differences in milk from clones that should have prompted further research.

Indeed, FDA's assessment seems at the outset designed to underestimate the food safety and animal welfare risks from cloning. The NAS recommended that FDA begin its assessment of cloning by identifying "the potential harms **regardless of likelihood.**"[iv][emphasis added] But in its report, when FDA cited this NAS advice the Agency left out the key phrase, changing their charge to "identify potential harms."[v] FDA also ignored the NAS advice that if cloned food enters the marketplace, it must be traceable[vi] – the agency has stated that it will not require labels on food from clones.[vii]

Since FDA could not find studies on milk or meat from clones, the Agency decided to assess the safety of these foods indirectly, by looking at other kinds of studies on cloning. FDA focused primarily on animal health, but many of the studies they reviewed reported little or no health data,

with researchers stating only that the animal clones "appeared healthy." Virtually none of these studies were designed or intended to look at the safety of food from clones or their offspring.

The FDA's indirect approach is deeply flawed. FDA's review finds so little data, and so many inconsistencies in the studies cited, that any safety conclusions are based more on faith than science. In fact, many scientists do not believe that cloning is an appropriate or suitable technology for raising food animals. In a 2005 meeting of cloning scientists, researchers summarized "Whether the technology [cloning] will become interesting from an agricultural point of view remains to be seen. There is no consensus on this subject among scientists."[viii]

Furthermore, FDA omitted or downplayed problems found in several studies it reviewed, even when these problems struck at the core of the agency's assumptions. For example:

- *FDA says that clones are genetically identical "twins" of their donors*. But studies found variation in clones greater than would be expected in "identical" animals[ix,x], and a recent science review stated, "clones are not exact copies of an already existing animal."[xi]

- *FDA says that defective clones, like other unfit animals, will be identified and removed from the food supply*. But scientists say that defects in clones can be hidden and undetectable, and could pose food safety risks.[xii] FDA found no studies that investigated the potential for food safety threats from unexpected new proteins or other metabolites in food from clones or their progeny. FDA also admits that even young clones that fall sick or die early could in some circumstances "be sent into the food supply."[xiii]

- *FDA claims that the cloning technology is improving, with better outcomes as the science advances.* But in the most recent studies cited, survival rate of clones was 68%, while earlier studies had a 79% survival rate. A 2005 science review found that "The success rates [in cloning] remain low (less than 5%)…."[xiv]

- *FDA says that defects in clones are different than those in other reproductive technologies only in degree.* But some common defects in cloning are rarely or never seen in normal reproduction. The incidence of one common cloning defect that often results in death of the clone and/or its surrogate, is as high as 42%, but in natural breeding or other assisted technologies the condition is extremely rare, with estimates as low as 1 in 7500.[xv] Following FDA's logic, a disease that causes cancer in 1 of 7500 patients is no different than one with a cancer rate of 1 out of 2½.

- *FDA claims that older clones have overcome any health anomalies and do not present any new health or food safety risks*. But cloning scientists have seen sudden illnesses and/or deaths in adult clones so often that one has termed it "adult clone sudden death syndrome."[xvi] Also, FDA admits that it almost no studies have been conducted for health or food safety from older clones.[xvii] In other words, for the period of the highest risk, FDA's safety conclusion is based on almost no data.

- *FDA says that clones will not be used for food but that most food will come from the progeny of clones, which are normal animals since reproduction "corrects" errors from the cloning*

process. But the NAS has questioned this assumption, stating "Little evidence is available in the scientific literature to assess whether the progeny of cloned animals are at increased risk for inherited or developmental defects."[xviii] A 2005 study of progeny of clones found that an abnormality from cloning that is usually assumed to be erased in progeny were instead reproduced in progeny.[xix] FDA also omits any analysis of research into the effect that DNA from mitochondria (mtDNA) can have on clones and their offspring. Several studies excluded by FDA have suggested that mtDNA could contribute to defects and low survival rates in clones and their offspring.[xx]

FDA's Risk Assessment: Review by Species

In its review, FDA's approach looks at animal health and food safety from a developmental perspective, organizing its analysis by stages of life from pregnancy to the mature, post-puberty period. Below, we review the FDA findings by species.[xxi]

Cows

FDA concludes that milk and meat from cloned cows is safe, but admits that "Few of the cattle clones are old enough to have been bred, given birth, and begun lactating."[xxii] FDA cites just three peer-reviewed studies on milk from clones. The largest of the three peer-reviewed studies, on milk from just fifteen clones, found significant differences in cloned milk[xxiii], and a smaller study found that one out of four clones produced 30% less milk.[xxiv]

For meat from cow clones, FDA cites no full peer-reviewed studies, but only brief reviews and data on eleven clones from the cloning company Cyagra. Despite the oft-repeated claim that meat from progeny and not clones will enter the food supply, FDA cites no studies and no data at all on milk or meat from the progeny of cow clones.

One milk study compared production by clones to their donor and concluded that milk production is only about 30% heritable.[xxv] Since producing dairy cows with higher milk production is a main reason cited for using cloning in dairy cows[xxvi], this study suggests that cloning will be of limited or no value to dairy farmers or and will not impact the price to consumers.

On animal health, FDA states that the unpublished data from Cyagra, the biotechnology company, is the most complete health data available,[xxvii] but the Cyagra clones exhibited many defects at a higher rate than would be expected randomly, including many defects associated with Large Offspring Syndrome (LOS).[xxviii] LOS is common in clones of cows, even among animals with birth weights within the normal range for their breed, and can include, among other abnormalities: respiratory, cardiac, hepatic, renal, umbilical, and immunologic problems; organ dysfunction (which can result in morbidity and often result in high mortality); pulmonary and cardiovascular abnormalities; delayed time to suckle and stand, hypoglycemia, forelimb flexor tendon contracture, enlarged umbilicus, and patent urachus (inability to excrete urinary waste).[xxix] Studies have found the incidence of LOS as high as 50% in cow cloning.[xxx]

FDA states that survival rates for clones are increasing, with mortality rates dropping to around 20% in recent studies.[xxxi] But a 2007 study on over 300 cow clones found that "On average, 42% of cloned calves died between delivery and 150 days of life."[xxxii]

A 2005 study cited by FDA, on semen quality from two clones, found clones had a lower pregnancy rate (55% compared to 63%) than natural comparators and almost double the rate of spontaneous abortions.[xxxiii] Other data sets submitted to FDA found semen quality was outside the normal range or marginal in semen from three of seven bull clones.[xxxiv]

For the post-pubertal period, at which animals would most likely enter the food supply, FDA cites just two peer-reviewed studies, one of which contains no health data.[xxxv] The agency thus relies on data on eighteen clones from the cloning company Cyagra for its evaluation of this important period. But Cyagra's data has troubling inconsistencies, finding significant differences in two hormones in clones versus controls.[xxxvi] The Cyagra data also fail to provide any accounting for twenty-eight clones that died past 18 months of age.[xxxvii]

Pigs

FDA cites no peer-reviewed studies comparing meat from cloned pigs to that from natural pigs, relying solely on data provided by the cloning company, Viagen. The Viagen data included information from just four of seven pig clones: two clones could not be used as they were "approximately" 100 pounds underweight, and one could not be used as it was condemned at slaughter. The surviving clones weighed less at slaughter, had less marbling and thinner backfat, and had darker, redder-appearing meat than meat from natural animals.[xxxviii]

FDA states that animal health data shows that cloned pig meat is safe. They cite two peer-reviewed studies to support this claim[xxxix], neither of which reported any health data. For reproductive health in pig clones, FDA cites a single peer-reviewed study using sperm from one clone boar. For the post-puberty period, the time during which clones would enter the food supply, FDA's review consists of a single sentence: "No reports on aging and maturity in swine clones were identified."[xl]

The agency thus relies entirely on Viagen's data for its safety claim. But the company's seven clones had a series of health problems, including severe diarrhea (six out of seven), influenza and a secondary infection, an inguinal hernia, sepsis (a blood infection), a swollen dewclaw, respiratory disease, cyanotic (bluish) skin color, and respiratory difficulties.[xli]

The agency also ignores health findings from other studies in its review which should have prompted further study of potential food safety and/or animal welfare issues in pig cloning. For example, FDA downplays a 2005 study that found 22 of 35 pig clones died in the first week of life, from a variety of troubling illnesses.[xlii] FDA omits the conclusion reached by the authors of this study: "Collectively our data indicate that the safety and long-term adverse biological effects of cloning must be further investigated."[xliii]

Goats

While most Americans do not think of goats as a meat source, dairy products from goats, especially goat cheeses, are a fast-growing food category in the U.S.[xliv] FDA cites no studies on the food safety of products from goats, finding that "No meat or milk composition data were identified for goat clones."[xlv] The agency uses only animal health data to suggest that food from cloned goats is safe, stating that "goat clones appear to be healthy, and do not appear to be materially different from conventional goats."[xlvi]

But FDA found little data in the literature on goat clones, as most of the few studies reviewed simply reported live-born animals, with no health data other than birth weight. For the post-puberty period, when goats are milking or would be slaughtered for meat, FDA found no health studies.[xlvii]

Perhaps most troubling, FDA appears to have intentionally omitted information from studies that contradict its conclusions of the health of goat clones. In its review, FDA repeatedly states that it found no studies that found abnormalities in goat clones similar to the Large Offspring Syndrome (LOS) problems found in cows or sheep, concluding that "**The only anomaly noted** [in goat clones] was…poor suckling response."[xlviii] [emphasis added]

But in fact, one of the most recent studies cited by the agency[xlix] found several LOS-like abnormalities in goat clones, including failure to initiate breathing, enlarged umbilical stumps, edema, and tendon laxity. FDA omits the authors' conclusion that "There was some evidence that as in other cloned species, there may be problems with placental development [in goat clones]."[l]

Similarly, FDA repeatedly states that goats are more easily cloned than other species, finding that another study showed a "100% success rate based on detectable pregnancy."[li] But the agency fails to paint the full picture: FDA does not report that the authors of this study actually found that the overall cloning efficiency was just 2.7%.[lii]

Progeny of Clones

FDA says that "Progeny of clones of any species are just like any other sexually produced offspring."[liii] The agency claims that problems in clones will not be found in progeny because reproduction will "reset even those residual epigenetic reprogramming errors that could persist in healthy, reproducing clones."[liv]

But a 2003 study not cited by FDA found that mammals can inherit certain epigenetic changes.[lv] Another recent study found that progeny of goat clones inherited shortened telomeres, directly contradicting FDA's assumption that defects in clones are erased in offspring of clones. The authors of the study state that while it is often assumed that abnormalities in clones are "erased" in reproduction, their findings from clone progeny

> …demonstrate that telomere length alterations incurred from the somatic cell cloning procedure may be transmitted through the germline to the next generation by conventional reproduction. [lvi]

The agency completely fails to address the uncertainty this finding raises regarding FDA's core assumption about progeny of clones, namely that they are somehow "corrected" in breeding.

FDA cites just four studies on progeny of cow clones, three of which reported no health data other than weight at birth. The fourth found differences in 4 of 13 blood levels and 4 of 15 clinical chemistry values in progeny versus comparator animals.[lvii] Data from the cloning company Viagen found that progeny of pig clones had more than twice as many abnormalities as normal animals,[lviii] while four percent of the progeny were destroyed due to weakness and unknown reasons, compared to none of the comparators.[lix] FDA found no health data on progeny of goat clones.

Recommendations

In October 2006, CFS and a coalition of consumer, religious, animal welfare and other groups filed a legal petition to FDA,[lx]calling for a mandatory pre-market review of food from clones based on the Agency's new animal drug process under the Federal Food, Drug and Cosmetic Act (FFDCA). Such a review would require rigorous safety testing before food from clones can be marketed, in the place of the current unscientific and biased "risk assessment" process. CFS therefore calls on FDA to **institute a mandatory moratorium on food or feed from cloned animals until:**

- The Agency has established a mandatory pre-market review process, regulating cloning as a new animal drug and requiring generational studies including investigations into potential food safety threats from unexpected metabolites potentially created by the cloning process;
- The troubling animal cruelty issues from cloning are resolved and cloning can meet the highest standards for animal welfare;
- Full "environmental impact statements" show no harmful environmental impacts from the use of cloning; and
- An Advisory Committee has addressed the many ethical issues around animal cloning, and broad public discussions have resolved the unique ethical and moral concerns raised by the technology.

Finally, if food from clones is deemed suitable for sale following the steps described above, FDA must require labeling of cloned food, to monitor for harmful effects (as advised by the NAS) and to protect consumers who wish to avoid cloned food.

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[i] Food and Drug Administration (2006). "Animal Cloning: A Draft Risk Assessment." December 28, 2006. (hereinafter referred to as "FDA RA")

[ii] FDA News Release, "FDA Issues Draft Documents on the Safety of Animal Clones," December 28, 2006, online at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01541.html

[iii] FDA has long been criticized due to similar conflicts in its drug approval divisions, with surveys of Agency scientists indicating the demise of the scientific process within the FDA; see for example, Union of Concerned Scientists, "FDA Scientists Pressured to Exclude, Alter Findings; Scientists Fear Retaliation for Voicing Safety Concerns," July 20, 2006, online at http://www.ucsusa.org/news/press_release/fda-scientists-pressured.html

[iv] National Academy of Sciences (2002). "Animal Biotechnology: Science Based Concerns.", p. 75

[v] FDA RA, Appendix A, p. A-4

[vi] National Academy of Sciences (2004). Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects. Subreport: Methods and Mechanisms of Genetic Manipulation and Cloning of Animals, p. 232

[vii] FDA, "Animal Cloning: FAQS About Cloning for Consumers," online at http://www.fda.gov/cvm/CloningRA_FAQConsumers.htm

[viii] Geir Tveit & Peter Sandøe (eds) (2005), "The Science and Technology of Farm Animal Cloning: A review of the state of the art of the science, the technology, the problems and the possibilities." Danish Centre for Bioethics and Risk Assessment, project report 6 (from the summary, online at http://www.sl.kvl.dk/cloninginpublic/index-filer/THESCIENCEANDTECHNOLOGYSummary.pdf)

[ix] Archer, et. al. (2003) "Hierarchical Phenotypic and Epigenetic Variation in Cloned Swine." BiolReprod, 69**,** 430–436

[x] Yonai et al (2005). "Growth, reproduction, and lactation in somatic cell cloned cows with short telomeres." J

Dairy Sci 88: 4097-4110, cited by FDA RA, p. 220
[xi] Geir Tveit & Peter Sandøe (eds) (2005), "The Science and Technology of Farm Animal Cloning: A review of the state of the art of the science, the technology, the problems and the possibilities." Danish Centre for Bioethics and Risk Assessment, project report 6, online at http://www.sl.kvl.dk/cloninginpublic/index-filer/CloninginPublicTechnicalReport.pdf, p. 24
[xii] NAS (2004), p. 222-228
[xiii] FDA RA, Appendix E, p. E-29
[xiv] Geir Tveit & Peter Sandøe (eds) (2005). p. 25
[xv] FDA RA, p. 111
[xvi] Jerry Yang, University of Connecticut, quoted in Sherry Morse, "Pig Heart Attacks Raise New Fears About Cloning," 2003 Animal News Center, Inc., online at http://www.buzzle.com/editorials/9-13-2003-45376.asp
[xvii] For example, FDA RA, p.127, p. 162-3.
[xviii] National Academy of Sciences (2004). Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects. Subreport: Methods and Mechanisms of Genetic Manipulation and Cloning of Animals, p. 222.
[xix] Betts, et.al. (2005). "Telomere Length Analysis in Goat Clones and Their Offspring." Molecular Reproduction and Development, 72: 461-470
[xx] St. John (2004). "The consequences of nuclear transfer for mammalian foetal development and offspring survival. A mitochondrial DNA perspective." Reproduction 127, 631-641; Lloyd, et. al (2006) "Aberrant Nucleo-cytoplasmic Cross-Talk Results in Donor Cell mtDNA Persistence in Cloned Embryos." Genetics, Vol. 172, 2515-2527; Takeda, et al (2003). "Takeda, et al (2003) "Proliferation of Donor Mitochondrial DNA in Nuclear Transfer Calves (Bos taurus) Derived From Cumulus Cells." Molecular Reproduction and Development, 64:429–437.
[xxi] Since FDA found that food from sheep clones would not be suitable for food, a review of FDA's findings on sheep clones is omitted.
[xxii] FDA RA, p. 248
[xxiii] FDA RA, p. 258-61
[xxiv] FDA RA, p. 262
[xxv] FDA RA, p. 262
[xxvi] See for example, Linda Bren, "Cloning: Revolution or Evolution in Animal Production?" FDA Consumer Magazine, May-June 2003, online at http://www.fda.gov/Fdac/features/2003/303_clone.html; Rick Weiss, "FDA Is Set To Approve Milk, Meat From Clones," *Washington Post*, October 17, 2006.
[xxvii] FDA RA, p.180
[xxviii] FDA RA, Appendix E, p. E11-13
[xxix] FDA RA, p. 118-122
[xxx] FDA RA, p. 115
[xxxi] FDA RA, p.117
[xxxii] Panarace, et al (2007). "How healthy are clones and their progeny: 5 years of field experience." Theriogenology 67:142–151.
[xxxiii] FDA RA, p. 142
[xxxiv] FDA RA, p. 145-7
[xxxv] FDA RA, p. 148-9
[xxxvi] FDA RA, p. 149-50; Appendix E, p. E30-1
[xxxvii] FDA RA, p. 201-202 and Appendix E, p. E6-8
[xxxviii] FDA RA, p. 278-9
[xxxix] FDA RA, p. 240
[xl] FDA RA, p. 163
[xli] FDA RA, Appendix F, p. F15-16
[xlii] FDA RA, p. 156-7
[xliii] Park, et al (2005). "A rare and often unrecognized cerebromeningitis and hemodynamic disorder: A major cause of sudden death in somatic cell cloned piglets." Proteomics 5: 1928–1939.
[xliv] See G.F.W. Haenlein (1996). "Status and Prospects of the Dairy Goat Industry in the United States." J. Anim. Sci. 1996. 74:1173–1181; also, Malinda Miller, "Dairy Goats." Iowa State University, Agricultural Marketing Resource Center, November 2006, online at http://www.agmrc.org/agmrc/commodity/livestock/goats/dairygoats.htm
[xlv] FDA RA, p.295
[xlvi] FDA RA, p.248
[xlvii] FDA RA, p. 172

[xlviii] FDA RA, p.295
[xlix] FDA RA, p. 171
[l] Behboodi, et.al. (2005). "Health and Reproductive Profiles of Malaria Antigen-Producing Transgenic Goats Derived by Somatic Cell Nuclear Transfer." Cloning and Stem Cells 7: 107-118
[li] FDA RA, p. 247
[lii] Reggio, et.al. (2001). "Cloned Transgenic Offspring Resulting from Somatic Cell Nuclear Transfer in the Goat: Oocytes Derived from Both Follicle-Stimulating Hormone-Stimulated and Nonstimulated Abattoir-Derived Ovaries" Biology of Reproduction 65, 1528-1533
[liii] FDA FAQS for Producers, online at http://www.fda.gov/cvm/CloningRA_FAQProducers.htm and FDA Cloning Myths, at http://www.fda.gov/cvm/CloningRA_Myths.htm
[liv] FDA RA, p.8
[lv] Rakyan, et. al. (2003) "Transgenerational inheritance of epigenetic states at the murine AxinFu allele occurs after maternal and paternal transmission." PNAS, vol. 100, no. 5, 2538-2543
[lvi] Betts, et.al. (2005). "Telomere Length Analysis in Goat Clones and Their Offspring." Molecular Reproduction and Development, 72: 461-470
[lvii] FDA RA, p. 151-2
[lviii] FDA RA, Appendix F, p. F-28.
[lix] FDA RA, Appendix F,, p. F-29-30
[lx] The petition is online at http://www.centerforfoodsafety.org/pubs/cloned_animal_petition10-12-06.pdf