



**FDA'S FLAWED APPROACH TO ASSESSING  
THE SAFETY OF FOOD FROM ANIMAL CLONES**

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**CENTER FOR  
FOOD SAFETY**

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# NOT READY FOR PRIME TIME:

## *FDA's Flawed Approach To Assessing The Safety Of Food From Animal Clones*

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## EXECUTIVE SUMMARY

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The Center for Food Safety has written this report, *“Not Ready for Prime Time: FDA’s Flawed Approach to Assessing the Safety of Feed from Animal Clones,”* in response to the Food and Drug Administration’s (FDA) 2006 risk assessment on food from animal clones. In its risk assessment, the FDA suggests that food from clones is safe, and while the agency claims this view is supported by strong science, this Center for Food Safety report actually shows that FDA found virtually no scientific studies to support the commercial release of these experimental foods. For example:

- ▲ FDA found no peer-reviewed studies on meat from cloned cows 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.

The report further finds that the FDA’s risk assessment is based on flawed assumptions and misrepresented findings. For example, the report shows that:

*1. Despite FDA’s claim that there is “no difference” between food from clones and their progeny and food from naturally-bred animals, most of the studies they*

*reviewed found troubling abnormalities and defects in animal clones which could pose food safety risks.*

- 2. Evidence from the Agency’s own report and from other scientists shows that cloning does not produce identical “twins” and that cloning therefore may not be useful in breeding. In fact, studies have found that clones from the same parent differ significantly from each other and from their parent animal. A recent scientific study concluded that scientists and breeders agree that cloning may not be useful for livestock production.*
- 3. The FDA review contradicts itself, first claiming that genetically defective clones will pose no risk to the food supply because the sick animals will be detected and removed, but then admitting that some sick and defective clones may in fact end up as food.*
- 4. FDA says the defects seen in clones also occur in natural reproduction, differing only by degree in clones, but the Agency also finds several defects in clones that are rarely or never seen in normal animals. For example, one common abnormality in clones that can result in stillbirth or early death—or death of the mother—occurs in normal cows only once in 7,500 instances, while it may occur in up to 42% of cloned cows.*
- 5. While the FDA claims that improvement in cloning technology is resulting in better success rates for clones, a 2005 scientific review found that success rates in cloning remain less than 5%.*

6. *FDA asserts that the offspring of clones—not clones themselves—will be used for food and that genetic defects in clones are “corrected” in the offspring. However, the National Academy of Sciences has questioned the validity of this assumption. Even more troubling, FDA downplays or omits from its assessment studies finding that some genetic defects in clones have been reproduced in clones’ offspring.*
7. *FDA has stated that it will not require labels on food from animal clones. But a 2004 National Academy of Sciences study noted that a national system to identify and track food from animal clones “must be implemented” before cloned foods are marketed.*

Based on these findings, the Center for Food Safety calls upon FDA to institute a mandatory moratorium on food or feed from cloned animals until:

- ▲ The FDA 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 National Academy of Sciences) and to protect consumers who wish to avoid cloned food.

## INTRODUCTION AND BACKGROUND

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The following Center for Food Safety report analyzes the Food and Drug Administration's December 28, 2006 paper, "Animal Cloning: A Draft Risk Assessment."<sup>1</sup> FDA launched its report with a press release stating that the Agency "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."<sup>2</sup>

But this Center for Food Safety 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 and on studies that make use of this same data, without noting the inherent conflict in basing regulatory conclusions so heavily on submissions by the companies who have a financial interest in FDA approval.<sup>3</sup>

### BACKGROUND

In 2006, between Christmas and New Years, the Food and Drug Administration (FDA) announced that it would soon approve the use of animal clones for the food supply. The Agency had previously released a "draft summary" on food from clones on Halloween in 2003, and at that time stated that although there were few studies on the subject, FDA believed that food from animal clones was no different than food from natural animals. So it was

not surprising that FDA reached this same conclusion in its 2006 risk assessment.

What is surprising is that so little new information is reported, and that from the start FDA seemed intent to underestimate the risks from cloned food. For example, the NAS proposed a framework for assessing the risks of food from animal clones, but FDA's risk assessment diverges from the scientific academy's guidance. In its report, FDA misstates *the first step* in risk assessment as outlined by NAS. In a chart labeled "Risk Analysis Steps as Described by the National Academy of Sciences," FDA states that the first step is to "identify potential harms."<sup>4</sup> But the NAS states that the first step in a scientific risk assessment is to "identify the potential harms *regardless of likelihood*."<sup>5</sup> [emphasis added.] The Agency does not disclose that it made this change nor provide any explanation for it, but by narrowing the terms of its risk assessment at the outset, FDA paved the way for a review that avoids a full assessment of many potential harms from cloned food.

FDA also states in its risk assessment that its responsibility includes "determin(ing) whether cloning poses any risk to animals involved in the cloning process."<sup>6</sup> In 2002, the Agency stated it would review cloning under FDA's authority to regulate new animal drugs, noting that animal safety issues are "definitely covered" under the New Animal Drug Act.<sup>7</sup>

But the Agency brushes aside massive evidence of harm to animals from cloning, stating that cloning defects are different only in degree from defects seen in animals bred

by other techniques. In fact, FDA found that some defects occur thousands of times more often in cloning than in other reproductive methods. Despite its earlier pledge, FDA failed to apply its new animal drug process to reviewing risks from cloning, which would have subjected the technology to more rigorous scientific scrutiny. Moreover, while FDA pledged in 2003 that it would consider ethical issues before allowing the sale of food from clones,<sup>8</sup> the Agency now claims that its jurisdiction “does not extend to ethical issues related to animal cloning.”<sup>9</sup>

The Agency has also stated that cloned food will not require labeling,<sup>10</sup> despite advice from NAS on the need

for monitoring and tracking cloned food if it is to be released into the market. In a 2004 paper, NAS warned that

A challenge to regulatory oversight of cloned and transgenic animals is development and implementation of effective programs to monitor the presence of these animals....Due to the possible need to differentiate cloned, transgenic animals, a national system for animal identity and identity preservation is required. This system must be implemented at the point of slaughter or processing to rapidly and inexpensively identify the presence of cloned, transgenic animals or products derived from these animals.<sup>11</sup>

## FDA'S FLAWED APPROACH

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The FDA claims that the scientific evidence shows that food from clones is no different than other food. But any attempt to evaluate the current science on the food safety of products from clones is doomed to fail, as there have been virtually no peer-reviewed scientific studies designed for evaluating cloned food. For example:

- ▲ 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.

Yet despite the lack of studies, the Agency's draft found that meat and milk from all of these cloned animals and their progeny are "as safe to eat" as food from natural animals. Moreover, even though many studies show troubling health data in clones that appear healthy, 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.

Since FDA could not find studies on milk or meat from clones, the Agency chose to assess the safety of these foods indirectly, by looking at studies that investigated basic issues about the cloning technology. FDA focused primarily on animal health information (referring to this

method as a "Critical Biological Systems Approach" or CBSA), even though many studies 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. But even if one assumes that this approach is valid, the Agency's review finds so little data, and so many inconsistencies in the studies cited, that any food safety or animal welfare 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."<sup>12</sup>

This leaves FDA in the position of extrapolating results from basic experiments to the entirely different and far more complex purpose of food safety. It also leaves the Agency with a paradox: FDA admits that most studies included only newborn and young clones; these studies found a host of defects, abnormalities, and troubling and/or unexplained health problems in clones. But, FDA says that this does not represent a food safety risk, since these animals are too young to be used for food. The Agency argues that older clones do not exhibit these health problems, and that this is the period that most animals would be used for milk or meat. But for the later developmental stages, FDA admits that there are few or no studies on the health of clones or their offspring.

For the post-puberty period in cow clones, for example, FDA says that “Most of the possible food consumption risks arising from edible products of clones (e.g., milk or meat) would occur during this Developmental Node,” but the Agency notes that “little information is available on animals during this developmental phase, and much of that information comes in the form of single sentences or short mentions in journal articles that address some other issue.”<sup>13</sup> For this same period in pigs, FDA found that “No reports on aging and maturity in swine clones were identified.”<sup>14</sup> In other words, for the period of the highest risk, FDA’s safety conclusion is based on almost no data. For health data on progeny of clones, FDA cites no peer-reviewed studies in pigs or goats. For progeny of cow clones, FDA found just six studies (plus one on transgenic cows), but five of these reported no health data other than weight at birth, and the sixth found significant differences in certain blood levels and clinical chemistry values in progeny versus comparator animals.<sup>15</sup> Unpublished data from the cloning company Viagen found that progeny of pig clones had more than twice as many abnormalities as normal comparator animals.<sup>16</sup>

FDA also 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 a 2003 study of cloned pigs found “a greater degree of variation in susceptible traits than expected for genetically identical animals.”<sup>17</sup> Data from a cloning company show that three clones from the same donor had weights at five months ranging from 197 to 282 pounds.<sup>18</sup> Another study showed that cow clones from the same donor produced significantly variable milk levels, different than their donor or each other.<sup>19</sup> A recent science review discussing barriers to the use of clones in agriculture stated,

Some of these barriers are connected with the fact that clones are not exact copies of an already existing animal... Doubts were therefore raised both from a scientific and breeder perspective as to whether the technology could

produce copies of animals with desired traits for the breeding industry.<sup>20</sup>

▲ **FDA says that defective, sick or diseased 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.<sup>21</sup> A 2007 study found differences in meat and milk from clones, and stated that “although these clones appeared to be physiologically normal, the composition of their [meat and milk] products might be slightly different.”<sup>22</sup> FDA also admits that even young clones that fall sick or die early could in some circumstances “be sent into the food supply,”<sup>23</sup> and that some health problems found in clones “are not conditions that typically exclude animals from food use...”<sup>24</sup> These alarming findings underscore the need for studies into the potential for food safety threats from unexpected new proteins or other metabolites in food from clones or their progeny, but FDA’s review found no such studies.

▲ **FDA claims that the cloning technology is improving, and harmful outcomes for animals are diminishing as new methods are developed and the science advances.**

But the Agency’s own data shows otherwise: in the most recent studies, survival rate of clones was 68%, while earlier studies had a 79% survival rate.<sup>25</sup> A 2005 science review found that “The success rates [in cloning] remain low (less than 5%) no matter what [the] methodology,”<sup>26</sup> and an article in the *New England Journal of Medicine* stated that “it may be exceedingly difficult, if not impossible, to generate healthy cloned animals...”<sup>27</sup>

▲ **FDA says that defects in clones are found in all other reproductive technologies, and differ only by degree.**

But two FDA regulators admitted in a January 2007 review of the Agency’s risk assessment that FDA had little evidence to support this conclusion, stating

The apparent frequency of those [animal health] risks at this stage of the development of



the technology, based on the published literature, is quantitatively higher [for cloning] than reported for other assisted reproductive technologies (ARTs). Given the nature of the available data, relatively small numbers of animals, the relatively small numbers of publications surveying animal health...the degree of confidence that can be placed in the overall estimates of incidence of adverse outcomes for either [cloning] or other ARTs over time is low.<sup>28</sup>

FDA also admits that cow cloning is unique among assisted reproduction, in that “pregnancy losses occur at all stages of gestation.”<sup>29</sup> Furthermore, the incidence of certain defects in clones is so much higher than in other techniques that FDA’s argument seems callous and unconvincing. For example, studies have found that Large Offspring Syndrome (LOS) occurs in up to 50% of clones,<sup>30</sup> but is rare in other reproductive techniques. The rate of hydrops, an abnormality that can lead to stillborn animals, early death, and/or death of the surrogate cow, is as high as 42% in cloning, but in natural breeding or other assisted technologies the condition is extremely rare, with estimates as low as 1 in 7500.<sup>31</sup> Following the Agency’s logic, a condition that causes cancer in 1 out of 2.5 patients is different “only in degree” from one with a cancer rate of 1 out of 7500.

▲ **FDA claims that older clones have overcome any health anomalies and can be considered no different than other animals if they survive past six months.**

But several findings of sudden illnesses and/or deaths in adult clones contradict this assumption. Cloning sci-

entists have seen the problem so often that one has termed it “adult clone sudden death syndrome.”<sup>32</sup> One study cited by FDA reported the sudden death of a cloned cow at 25 months old,<sup>33</sup> and data submitted to FDA by a cloning company shows that 28 clones died past 18 months old.<sup>34</sup> Other documented accounts of apparently “healthy” clones dying suddenly and unexpectedly are numerous.<sup>35</sup> FDA fails to address this troubling phenomenon in any detail.

▲ **FDA says that clones will not be used for food but that most food will come from the progeny of clones. The Agency argues that the progeny are “normal” animals since reproduction “corrects” errors from the cloning process.**

But a 2005 study of progeny of clones found that an abnormality (shortened telomere length) from cloning that is usually assumed to be erased in progeny was instead reproduced in progeny.<sup>36</sup> A 2004 study stated that mutations from the less obvious defects in clones could be passed on to the progeny, concluding that “...such problems could lead to inheritable anomalies among clones and their offspring.”<sup>37</sup> The NAS also questioned the certainty of FDA’s 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.”<sup>38</sup> In fact, research into the effect that DNA from the inserted egg cell (mitochondrial DNA, mtDNA) can have on clones and their offspring has suggested that this mtDNA could contribute to defects and low survival rates.<sup>39</sup> FDA fails to address these scientific contradictions to its core assumption about the progeny of clones.

## FDA'S RISK ASSESSMENT: REVIEW BY SPECIES

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In its risk assessment, FDA's CBSA approach looks at animal health and food safety from a developmental health perspective, organizing its analysis by stages of life from pregnancy to the mature, post-puberty period. Below, we review the FDA findings by species,<sup>40</sup> supplementing our analysis with information that takes a closer look at some of the original papers cited by FDA and from studies not mentioned by the Agency.

### COWS

#### FOOD SAFETY STUDIES ON COW CLONES AND THEIR PROGENY

For cows, FDA admits that there is little information on milk safety, since “few of the cattle clones are old enough to have been bred, given birth, and begun lactating.”<sup>41</sup>

Nonetheless, the Agency concludes that “milk from cow clones does not appear to differ significantly in composition from milk from non-clones.”<sup>42</sup> FDA cites three full peer-reviewed studies, “summary comments” from an abstract (on milk from two clones), an unpublished summary translation of a Japanese study, “brief” reports, and a preliminary report to support this conclusion.<sup>43</sup> In one of the three peer-reviewed papers, one out of four clones in the study had 30% lower milk production (which FDA calls “expected” since the clone gave birth prematurely).<sup>44</sup> The largest of the three studies, on milk from fifteen cow clones, found significant differences in two fatty acids and four minerals.<sup>45</sup>

The third study, on milk from ten clones, found differences in milk production from clones compared to their

donor and concluded that milk production is only about 30% heritable.<sup>46</sup> Since producing dairy cows with higher milk production is a main reason cited for using cloning in dairy cows,<sup>47</sup> this study suggests that cloning will be of limited or no value to dairy farmers and will not impact the price of dairy products to consumers.

FDA also reviewed a seven-page unpublished “summary translation” of a Japanese study of cloned milk. FDA reports that a test in rats of the digestibility of cloned versus natural milk found equal rates of digestion, but the Agency's chart from the study shows the rate in ordinary cattle as  $83.0 \pm 2.6$ , while the clones' rate is stated as  $8.13 \pm 3.4$ .<sup>48</sup>

As “additional data”, FDA cites a “preliminary report” of a three-week long rat feeding study, and brief data from two reports assessing milk from six clones derived by a New Zealand research group. In one study, the group found statistically different levels of two fatty acids and one protein in the clones' milk, and in a report a year later, these levels were again statistically different. In the later report, levels of bovine serum albumin, a protein in milk, was markedly higher in clones' milk, at  $162 \pm 6$  mg/L, compared to 105 mg/L for the donor cow.<sup>49</sup>

For meat from cow clones, FDA cites no full peer-reviewed studies. The Agency reports on one published summary of data translated from the Japanese study,<sup>50</sup> a study on milk that also looked at meat from two clones, and data from eleven clones produced by the biotechnology company Cyagra. The Agency reports that “no biologically significant differences” were observed in the

Japanese research, but their chart shows that cholesterol and fats were as high as or higher in clones than the maximum value in ordinary cattle, while protein in clones was lower than the lowest value.<sup>51</sup> Similarly, Cyagra's data shows higher levels of several fatty acids, as well as higher total fat and saturated fatty acids than natural comparators.<sup>52</sup> In the other study, on meat from two clones, the authors found twelve instances where the clones and genetic comparators showed differences.<sup>53</sup>

Despite the oft-repeated claim that food from progeny, and not clones, will enter the food supply, FDA cites no studies and reports no data at all on milk or meat from the progeny of cow clones.

Two papers from January 2007, published concurrently with an FDA paper on its risk assessment, are instructive. One paper, on milk from two groups of clones, found that "milk from each of the cloned groups was of different composition," and concluded that "the evaluation of larger and broader datasets will be necessary to provide the assurance for regulators and the consumer that food products from clones and their progeny are safe to eat."<sup>54</sup> The other paper, on milk and meat from clones, found significant differences in the fatty acid composition of milk and meat from two families of clones, and noted that the data "in both milk and muscle suggested that changes occurred in the tissues and although these clones appeared to be physiologically normal, the composition of their products might be slightly different."<sup>55</sup> The authors concluded:

*Our view is that the establishment of a larger framework for multidisciplinary research in emerging topics such as animal cloning should still be considered as a prerequisite before analysing the risk management of food products derived from this biotechnology.... If the products of clones (and most probably from clone offspring) are susceptible to entering the human food chain, further research should be shared worldwide, remain transparent and open to debate for consumers.<sup>56</sup> [emphasis added]*

## ANIMAL HEALTH: FOOD SAFETY RISKS AND ANIMAL WELFARE CONCERNS

FDA admits that "Very few [studies] systematically evaluate the health of the animals, many simply state that 'animals appear normal and healthy' or that 'no differences were observed between clones and controls.'"<sup>57</sup> The Agency further notes that the unpublished data from the cloning company Cyagra is the most complete health data available.<sup>58</sup>

In the Cyagra data, many defects were found at a higher rate than would be expected randomly,<sup>59</sup> including pre-pubescent mammary development, lung sounds, cryptorchidism, and cardiac arrhythmias, among others.<sup>60</sup> While FDA says that defective clones will be condemned at slaughter and will not go into the food supply, the Agency states that some defects "are not conditions that typically exclude animals from food use...with respect to animal safety, these [health] conditions may pose some cause for concern."<sup>61</sup> FDA offers no explanation or plan for detecting hidden defects that scientists say can linger in clones.

Hydrops, an abnormality common in cloning in which fluid builds-up in the fetus and/or placenta, can lead to abortion, stillbirths, or early deaths of clones, and usually results in euthanasia of surrogate cows. The incidence of hydrops in cloning 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.<sup>62</sup> FDA repeatedly states that it finds that cloning is safe for livestock based on the notion that safety issues in clones are "no different" than those found in other breeding techniques, but hydrops is a stark example of the absurdity of this reasoning. Following the Agency's logic, a condition that causes cancer in 1 out of 2.5 patients is no different than one with a cancer rate of 1 out of 7500.

Large Offspring Syndrome (LOS) is also common in clones of cows. LOS can manifest in multiple abnormalities, even among animals with birth weights within the normal range for their breed. Health problems from LOS can include, among others: respiratory, cardiac, hepatic,

renal, umbilical, and immunologic problems; systemic abnormalities (including organ dysfunction, which can result in morbidity and often result 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 (failure of the ductus arteriosus to close after birth resulting in extra blood flow to the lungs) and ventricular defects; delayed time to suckle and stand, hypoglycemia, forelimb flexor tendon contracture, enlarged umbilicus, and patent urachus (inability to excrete urinary waste).<sup>63</sup>

A large 2007 study by Cyagra researchers reported just 317 live births out of 3374 cloned embryos, while after 150 days only 225 cloned calves were still alive.<sup>64</sup> The most common abnormalities found in the live-born clones were indicative of LOS, and included enlarged umbilical cords (in 37% of clones), respiratory problems (19%), contracted flexor tendons (21%), and others.<sup>65</sup> In its review, FDA fails to assess the frequency of LOS across studies of cow cloning, but studies have found the incidence of LOS as high as 50% in cow cloning.<sup>66</sup> The Agency states but fails to comment on the animal welfare implications inherent in its finding that

The survival rate of clones [in the perinatal period] appears to be in the range of 5 to 18 percent, depending on how it is calculated. Many of the perinatal clones die of complications or sequelae of LOS. Newborn cattle clones may be more physiologically fragile than their comparators....<sup>67</sup>

#### *FOOD SAFETY AND ANIMAL WELFARE: COW CLONES BY DEVELOPMENTAL PERIOD*

##### *PREGNANCY*

FDA notes that cow cloning is unique among assisted reproduction, in that “pregnancy losses occur at all stages of gestation.”<sup>68</sup> FDA acknowledges the high failure rate in cow cloning, noting a range of estimates of “successful” cloning attempts from one in 1,000 (from embryos implanted to live births) to one in four (based on pregnancies confirmed at 60 days, and thus significantly

inflated).<sup>69</sup> The Agency states that “few detailed descriptions of placentae of cattle clones exist,”<sup>70</sup> but the findings of the three studies cited all show problems. In one study, researchers found that the numbers of cotyledons were reduced in clone fetuses<sup>71</sup> (in ruminants, the cotyledon is the fetal parts of the placenta where nutrients and wastes are exchanged); a second found that “all clone placentae exhibited one or more abnormalities of varying severity: moderate to severe edema, enlarged vessels, adventitious placentation, and large areas devoid of placentomes. No abnormalities were described for the comparator placentae collected.”<sup>72</sup> The third study found that cow clones “had poorly developed cotyledons” and other abnormalities.<sup>73</sup>

In a study comparing cloning to IVF and other reproductive technologies, FDA notes that clones showed a pregnancy loss incidence of approximately 44 percent, while none of the IVF pregnancies were lost.<sup>74</sup> In an Appendix that compares different breeding technologies, FDA concludes that “the adverse outcomes noted with [cloning] are not unique, but are of concern due to their increased frequency.”<sup>75</sup>

##### *PARTURITION*

FDA describes hydrops, a common problem in cow clones involving abnormal fluid build-up (edema) in the placenta and/or fetus. Hydrops can lead to abortion, stillbirths, or early deaths of clones, and “most studies that discussed outcomes indicated that dams developing hydrops were euthanized.”<sup>76</sup> In other assisted technologies, only one study showed any incidence of hydrops (1/200, or .5%), but in clones, the incidence of hydrops ranged from 13 to 42%.<sup>77</sup> Hydrops in natural breeding is estimated to be 1 in 7500.<sup>78</sup>

The Agency also describes dystocia, or difficult labor, which can result from oversized fetuses (among other possible causes). FDA reports high mortality rates for LOS clones, and notes that “Stress associated with dystocia, prolonged labor and emergency C-section birth is a risk factor for large calves.”<sup>79</sup> Other problems found in studies on cow clones in this period include weak or non-existent uterine contractions, poor mammary development and failure to lactate.<sup>80</sup>

*PERINATAL PERIOD*

FDA notes that “early reports, beginning in 1998, of clone mortality rates were 50 to 80 percent,” but states that more recent studies show better results, with mortality rates dropping to around 20%.<sup>81</sup> FDA refers to its chart of “survival rates” of cow clones to support this conclusion.<sup>82</sup> But omitting three early studies in the chart, the data actually shows that recent cow cloning studies reported a higher mortality rate than those of a few years ago. In studies dated 2004 and 2005 (the most recent studies shown), the combined survival rate of cow clones was 68% (170 of 252), while studies from 2000 to 2002 had a 79% survival rate (169 of 214).<sup>83</sup> If anything, then, *this table indicates that survival rates in cow cloning have been decreasing lately*. In fact, a 2007 study of more than 300 cow clones found that, “on average, 42% of cloned calves died between delivery and 150 days of life.”<sup>84</sup>

In its analysis of data from the cow cloning company Cyagra, FDA states that birth weights were only available for 34 of 123 live-born clones, noting that “eighteen of the 34 (53 percent) birth weights were at least 20 percent above the average for their breed... Fifty-five additional calves that were not oversized at birth, or for which birth weights were not available, showed clinical signs often associated with LOS.”<sup>85</sup>

More simply put, in Cyagra’s data 73 of 123 (58%) live-born clones were significantly overweight and/or showed signs of LOS. Seventeen of these 73 clones died within 48 hours of birth.<sup>86</sup> This data contradicts FDA’s public statements that “As producers understand more about the cloning process, the rate at which LOS is observed in clones has been decreasing.”<sup>87</sup> Cyagra’s data also found that

Three of the ten calves died or were culled... The major classes of adverse outcomes noted for neonates included stillbirth, umbilical bleeding/abscess/management, colostrum/passive transfer problems, and euthanasia for defects (renal, circulatory, tendon contracture, placental abnormalities, cardiac, abomasal, and ascites [increased fluid in the abdomen]).<sup>88</sup>

In an example of a study showing what FDA calls “successful production of clones,”<sup>89</sup> the authors report that 14

of 35 clones (40%) were stillborn and another three aborted, apparently near term, most with LOS symptoms. The researchers found a pregnancy rate in clones of about 30%, compared to nearly 53% for IVF-comparators. Body weights for all the surviving clones were significantly higher than comparators, with 12.5% of clones higher than the heaviest comparator.<sup>90</sup> Another study of clones from a donor cow that was ten years old found that at birth the clones had “*an adult appearance, displayed as many wrinkles in the skin, thickbone structure and rough hairs resembling those of adult males.*”<sup>91</sup> [emphasis in FDA RA]

*JUVENILE DEVELOPMENT*

FDA notes that for the post-weaning period, “less detailed information has been published on the health of bovine clones.”<sup>92</sup> The Agency cites USDA figures showing annual mortality among natural and AI produced calves of 2.4%,<sup>93</sup> but for clones, a large 2004 study found annual mortality of at least 8%.<sup>94</sup> Referring to this study, FDA states improbably that “Sixty seven percent of these calves (89 animal clones) survived to weaning (3 months of age) and 81 percent of the calves (72 animal clones) survived postweaning.”<sup>95</sup> Here FDA is playing with numbers—the actual post-weaning survival of the 123 calves was 54% (72 of 123).

Another study reported that about “30% of the cloned calves die before reaching 6 months of age, with a wide range of pathologies.”<sup>96</sup> In natural breeding, the rate is about 5%.<sup>97</sup>

FDA reports on one study which concluded that even “apparently healthy” clones should not be considered “physiologically normal” until at least two months of age.<sup>98</sup> But evidence suggests that many uncertainties exist even after that age (see below). Another study found lower levels of the hormone IGF-1 in these same cow clones.<sup>99</sup>

Cyagra’s data also showed problems in juvenile clones. Their clones suffered from “an increased incidence of umbilical problems (*e.g.*, enlargements, excessive bleeding, oomphalitis (navel infection), tendon contracture, and cryptorchidism. Clones had umbilical extirpation (surgical removal of tissue) at a much higher rate than comparators.”<sup>100</sup> FDA states that “This increase represents a real risk to

clones...,” but otherwise fails to address this animal welfare concern.<sup>101</sup> Cyagra’s data also showed that three clones from the same donor were remarkably different, with weights at about five months ranging from 197 to 282 pounds, casting doubt on the notion that cloning creates “identical twins” (a fourth clone from this line died early of LOS).<sup>102</sup>

#### REPRODUCTIVE DEVELOPMENT

FDA reports on a study that found clones reached puberty at a later age than controls and had higher body weights at first estrus. One of the four clones failed to reproduce, with no cause determined.<sup>103</sup> FDA’s chart on “pregnancy rates for clone and comparator cattle” includes two (out of four) studies using transgenic and/or non-transgenic clones. In the two studies on non-transgenic clones, the pregnancy rate was 82%,<sup>104</sup> compared to a 90 to 95% average in the beef and dairy industries.

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.<sup>105</sup> A 2004 study found that the range of rates of development to blastocyst for embryos fertilized *in vitro* by sperm from six bull clones was lower than that of comparators, while pregnancy and calving rates of clones were 83%, compared to 90% for comparators.<sup>106</sup> Another study found overall pregnancy rate for three clones was 65%, with low average birth weight of the progeny.<sup>107</sup>

FDA also reviewed studies of semen from bull clones. In one it found “Differences in semen volume were inconsistent,”<sup>108</sup> while another found that the percent of normal sperm was consistently lower in three clones compared to sperm from the donor (the lowest was 67%, compared to 86.5% for the donor), and cleavage rates were also lower for all three (with the lowest at 54.6% compared to 75.2% for the donor). FDA misleadingly reports, “percentages of normal sperm were not statistically different...cleavage rate and development to blastocyst were not statistically different.”<sup>109</sup> In other reports on semen evaluations from bull clones, FDA notes that in one data set, semen quality in two out of four clones was unacceptable or marginal, while another set found one of three clones produced semen outside the normal range.<sup>110</sup>

#### POST-PUBERTAL PERIOD

FDA reports on a study of nine clones that found several blood levels differing in clones versus comparators. The Agency also cites a study that found survival past six months, but with no health data reported.<sup>111</sup> The Agency also reports on unpublished data from two clones, showing some differing levels, and on Cyagra’s data on eighteen clones, showing significant differences in the hormones IGF-1 and E2.<sup>112</sup> One of the eighteen Cyagra clones was further characterized as “a dwarf with frequent bloat.”<sup>113</sup>

FDA states that Table E-2 in its Appendix on Cyagra’s data shows “the information on samples taken from calves within the first 24 hours of birth,”<sup>114</sup> but the table actually lists outcomes of 39 clones that died between birth and 150 days. The Table is titled “Summary of Outcomes for Clones Not Surviving Birth,” although the table includes information on 13 animals that did survive birth, including one clone that survived to 149 days.<sup>115</sup>

But even more disturbing, the table and Cyagra’s accounting show unexplained losses of many adult clones. FDA states that 103 Cyagra clones were alive at 3 days old. The Agency states that 67 (of the original 134) animals were alive when the data was collected. In the Cyagra appendix, FDA says that eleven of the clones that were alive at 48 hours died “within approximately 1.5 years later,”<sup>116</sup> leaving 95 clones alive—although earlier FDA noted that the deaths of these clones extended only to the 149th day.<sup>117</sup> Regardless, there is an unexplained discrepancy between the 95 clones alive at 1.5 years (at the latest) and only 67 alive at the time of sampling, leaving 28 clones (29% of those alive at 1.5 years) unaccounted for and presumed dead between 1.5 years and the time of sampling.<sup>118</sup>

#### PROGENY OF COW CLONES

FDA states that “almost all of the production animals (i.e., sources of meat and milk) from the overall [cloning] process are likely to be sexually-reproduced progeny of clones.”<sup>119</sup> 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.”<sup>120</sup> But a 2003 peer-reviewed study not cited by FDA found that progeny of mammal clones can inherit certain epigenetic

changes,<sup>121</sup> and the NAS has stated that “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.”<sup>122</sup> FDA cites just four studies on progeny of clones, three of which reported no health data other than birth weight. The fourth found differences in 4 of 13 blood levels and 4 of 15 clinical chemistry values in progeny versus comparator animals.<sup>123</sup>

FDA also omits studies investigating the potential for problems in clones and their offspring from mitochondrial DNA (mtDNA). In natural reproduction, DNA transmitted to the offspring derives not only from the egg cell’s nucleus but also from mitochondria, which surround the nucleus. But in cloning, mtDNA can come from the animal that serves as the source of the enucleated egg as well as from the animal from which the nucleus derives. Thus, unlike natural animals, clones can inherit a combination of mtDNA from two mothers, with unexpected effects on the cloned offspring. FDA has only one sentence on this problem in its risk assessment, suggesting that any problems derived from mtDNA in clones are “speculation” and claiming that “only one study was identified that looked specifically at mitochondrial effects on embryo development (Takeda et al. 2005).”<sup>124</sup>

But in this and other papers, several earlier studies are cited as demonstrating the inheritance of mtDNA in cow clones.<sup>125</sup> FDA also omits several other studies that indicate that mtDNA could create problems in clones. One study noted that mtDNA can impact milk quality in dairy cows and carcass traits and fertility in beef cattle.<sup>126</sup> Others have shown that mtDNA can be inherited in clones and their offspring,<sup>127</sup> and another study suggested that mtDNA could contribute to the common defects and low survival rates in these animals.<sup>128</sup> One recent paper stated “The degree of donor mitochondrial DNA transmission appears to be random and currently no evidence exists to explain this phenomenon,” further noting that persistence of mtDNA has been observed in cloning “but not in those embryos generated through in vitro fertilization,”<sup>129</sup> contradicting FDA’s assertion that problems in cloning are no different than other reproductive technologies. Mitochondrial inheritance has also been shown to be a

factor in certain inherited diseases.<sup>130</sup> FDA completely fails to assess or report on the food safety or animal welfare risks from this problem in clones and their progeny.

## PIGS

### FOOD SAFETY STUDIES ON PIG CLONES AND PROGENY

FDA cites no peer-reviewed studies comparing meat from cloned pigs to natural pork. Instead, FDA notes that the cloning company Viagen worked with the Agency “to designed (sic) two experiments that produced data comparing meat composition” of clones to natural animals.<sup>131</sup>

The Viagen data included information from just four pig clones. Three others were excluded from the study: two clones could not be used because they were “approximately” 100 pounds underweight, and one could not be used because it was condemned at slaughter. Even excluding these animals, carcasses from the Viagen clones weighed on average more than ten pounds less than those from the natural pigs. Backfat thickness was also greater for the natural animals, and the meat from clones was “slightly darker and more red” than natural meat.<sup>132</sup>

On meat composition, FDA notes only that “differences in meat nutrient composition were very small....”<sup>133</sup> But its chart comparing nutrient levels in cloned versus natural pigs shows clones have lower levels of all except one amino acid, while cholesterol and all except two fatty acid levels were higher for clones.<sup>134</sup> The Agency offers no explanation or discussion of these findings.

FDA also cites no peer-reviewed studies on meat from progeny of pig clones, but again relies on data from Viagen. As in the Viagen clones, differences in backfat thickness and meat color were noted for progeny versus natural comparator animals.<sup>135</sup>

### ANIMAL HEALTH: FOOD SAFETY RISKS AND ANIMAL WELFARE CONCERNS

FDA states that its conclusion that food from pig clones is safe from an animal health perspective is “drawn largely

from the animal health information presented by Walker et al. (2002), Archer et al. (2003b), and the Viagen dataset....<sup>136</sup> But Walker provided no health data other than birth weights (which were low for clones), and Archer's is neither a health nor a food safety study, but rather looked at the *behavior* of clones. FDA's "safety" conclusion, therefore, is essentially based entirely on data from Viagen, a cloning company that stands to benefit from FDA's approval of cloned food. Moreover, FDA stated that the limitations in Viagen's study design, data reporting, and findings of altered nutrient levels in clones "diminish the confidence" of the Agency's food safety determination.<sup>137</sup>

Indeed, the Viagen data is sorely lacking. The company studied just seven clones, three of which were described as "poor doers" that were excluded from the final carcass analysis<sup>138</sup> because they were diseased and/or severely underweight. Viagen's clones showed lower blood levels of two important hormones, IGF-1 and estradiol, and took nearly a month longer to reach target slaughter weights and weighed less at slaughter than natural animals.<sup>139</sup> Organ weight as a percentage of body weight was also smaller for clones.<sup>140</sup>

Other data on pig clones show serious health and safety issues that FDA does not adequately address.<sup>141</sup> One study reported several health parameters, finding significant differences and epigenetic changes in "normal" appearing clones.<sup>142</sup> Another of the most recent papers on pig cloning found that "25% (7/28) of [cloned pigs] showed severe congestion of lung and liver or neutrophilic inflammation in brain indicating that unexpected phenotypes can appear as a result of somatic cell cloning."<sup>143</sup> In this 2005 study, 22 out of 35 cloned pigs died within the first week of life (another five died at birth) after suffering numerous health problems, including cerebromeningitis, diarrhea, leg and face abnormalities, male pseudohermaphroditism (Leydig cell hypoplasia), and others. The authors conclude that "Collectively our data indicate that the safety and long-term adverse biological effects of cloning must be further investigated."<sup>144</sup>

## *FOOD SAFETY AND ANIMAL WELFARE: PIG CLONES BY DEVELOPMENTAL PERIOD*

### *PREGNANCY AND PARTURITION*

FDA states that "it is difficult to draw conclusions regarding fetal loss in clone-bearing swine pregnancies," but the Agency later acknowledges that "Most pregnancies fail to reach term, despite efforts to support surrogate sows hormonally or with co-transfer of IVP or parthenogenic embryos."<sup>145</sup> In fact, every study FDA reviewed found significant pregnancy losses and difficulties to establish and complete pregnancies in pig cloning.<sup>146</sup> FDA admits that success rates in pig cloning "are low even when compared to reports of cloning in other species."<sup>147</sup> One of the most recent studies found that fewer than one in 200 cloned embryos survived to birth,<sup>148</sup> rebutting FDA's claim that as the technology improves success rates are increasing.<sup>149</sup>

Interestingly, at a European conference on cloning in May 2005, Viagen's CEO Scott Davis presented his company's unpublished findings that "far surpassed any previously published success rates" in pig cloning, claiming to have achieved births of "around 15 piglets for every 25 blastocysts inserted."<sup>150</sup> But no such Viagen data was described by FDA, and no data at all on overall success rates is given in the lengthy Appendix on Viagen's cloning studies.

FDA states that studies on pig clones "did not report any complications with delivery,"<sup>151</sup> but since most of these studies do not discuss delivery at all, this statement is misleading. In fact, in one of the five studies cited by FDA, clones were delivered by Caesarean section<sup>152</sup> (a technique often used because of delivery complications), as were all seven Viagen clones. The Agency also notes that pig cloners have reported that "agalactia (failure to lactate) was noted in sows giving birth to piglet clones."<sup>153</sup>

### *PERINATAL PERIOD*

For pig clones during the perinatal period, FDA concludes that "piglet clones appear to be normal and healthy,"<sup>154</sup> even though the Agency cites no studies that report any health data on piglet clones, and admits that



“there are few detailed descriptions on health and vitality” of neonatal pig clones.<sup>155</sup> FDA draws this conclusion from studies that consistently found low birth weights in pig clones, and recorded only that live-born clones “appeared normal” (with some studies reporting only that clones survived birth). Five of the seven studies cited by FDA resulted in five or fewer live-born clones.<sup>156</sup> One of these studies found that two of four pig clones died within a week, and as noted above, a recent study found that 22 of 35 cloned pigs died within the first week (another five died at birth) after suffering numerous health problems. Other unpublished data submitted to the Agency found that two of five cloned piglets died within 48 hours of birth.<sup>157</sup> Viagen’s data includes no information on neonates, other than their low birth weights,<sup>158</sup> which is consistent with all of the peer-reviewed studies.

#### *JUVENILE DEVELOPMENT*

A number of problems were found in the Archer study<sup>159</sup> and Viagen data that FDA reviewed for the juvenile period for pig clones. Archer’s study used only nine clones: one had unusual hair growth, another had a skin condition (hyperkeratosis) that could condemn the pork skin at slaughter, a third was severely underweight and never attained normal weight, and a fourth had an unequal teat distribution. Of this last characteristic, FDA says only that “Teat number was the same for all except one clone piglet...”<sup>160</sup> But this conclusion contrasts with the study’s authors, who specifically note that this anomaly contradicts the assumption that clones are identical to their donors, stating that

We have seen this variation in number of teats in other clones generated by us but not used in this study....(C)lonal differences were observed in skin type, hair growth pattern, and number of teats, supporting the observation that cloning creates variation that is independent of genetic background.<sup>161</sup>

The Viagen data is replete with health problems, but FDA ascribes these to rearing deficiencies, and fails to analyze adequately the possibility that some or all of these problems could have derived from the cloning process. Viagen’s seven clones suffered from severe diarrhea (six of seven clones), influenza and a secondary infection, an

inguinal hernia, sepsis (a blood infection), a swollen dew-claw, respiratory disease, cyanotic (bluish) skin color, and respiratory difficulties.<sup>162</sup> FDA acknowledges that “clones had more health problems than comparators,”<sup>163</sup> but concludes only that “none of the swine clones exhibited any adverse outcomes that have not been observed in conventionally bred and reared swine.”<sup>164</sup>

#### *REPRODUCTIVE DEVELOPMENT*

For reproductive development of pig clones, FDA cites a single peer-reviewed study on reproduction from five clone gilts inseminated with sperm from one clone boar, and notes that “No other peer-reviewed reports have been identified to date on puberty and reproduction in male or female swine clones.”<sup>165</sup> The Agency also reviews Viagen data on reproduction using semen from four boar clones, finding that “litter size was more variable for boar clones, and mean litter size was slightly smaller for clones” than natural comparators.<sup>166</sup> The Viagen data found that nearly 28% of the clone litters had fewer than ten pigs, compared to just 4% of the natural animal comparators.<sup>167</sup>

#### *POST-PUBERTAL PERIOD*

FDA’s “Animal Health” section for the post-puberty period in pig clones consists of a single sentence: “No reports on aging and maturity in swine clones were identified.”<sup>168</sup> The Agency later repeats that it “was not able to identify any peer-reviewed studies on non-reproductive postpubertal studies (sic) in swine clones.”<sup>169</sup> Thus, the Agency relies solely on the Viagen data for this period, which, as noted above, consisted of data on just five clones, and found that clones weighed less than natural comparator animals and had reduced marbling and back-fat thickness.<sup>170</sup> Since pigs are slaughtered at this age, FDA’s assessment of pig clones at the very period they would enter the food supply relies entirely on data from a company seeking to benefit from FDA’s approval.

#### *PROGENY OF PIG CLONES*

FDA cites two studies, on a total of fourteen animals, and then states that “No other peer-reviewed reports have been published to date on progeny of swine clones.”<sup>171</sup> Of the two published studies, one followed the animals for just 21 days.<sup>172</sup> The other study, on progeny of nine clones, found significant differences in blood urea nitrogen

(BUN) at 15 weeks and alkaline phosphatase (ALP) at 27 weeks between clone progeny and their comparators.<sup>173</sup> Thus, for progeny of pig clones, FDA relies primarily on data from Viagen, which used four clones to produce progeny for their data. The Viagen data was reviewed in a 2007 study, but this analysis of the company's data had serious methodological flaws, which could have obscured significant differences.<sup>174</sup> In this review, the authors established an artificially expanded "normal range" of clinical values (by taking ten percent above the maximum range of comparators and ten percent below the minimum range), and calling any level from clones that fell into that range "normal." But this is a method designed to find the widest possible range of "normalcy"—if any of the control animals had outlying values, those values—plus or minus ten percent—would establish the range of normality! This could obviously conceal values in clones that would otherwise be considered abnormal.

In addition to the more variable and smaller litter size noted (in "*Reproductive Development*", above), the Viagen data had several troubling findings:

- ▲ Progeny of clones showed "substantial number of pigs" dying around the time of birth, with 25% of progeny of clones dying compared to 17% of comparator progeny;<sup>175</sup>
- ▲ Progeny of clones had an abnormality rate of 2.5 percent, versus 1% for comparators;<sup>176</sup>
- ▲ The total number of disposed pigs (stillborns, destroyed, overlays, unknown deaths and weak pigs) was 21 percent for the progeny of clones, compared to 14 percent for the comparators; four percent of the progeny were destroyed due to weakness and unknown reasons, compared to none of the comparators;<sup>177</sup>
- ▲ The percentage of animals reaching slaughter age was lower for progeny of clones (73%) than for comparators (81%),<sup>178</sup> and progeny of clones took an average of 5.6 days longer to reach slaughter weight.<sup>179</sup>
- ▲ In animals between 3 and 30 days old, eleven blood levels in 5% or more of the progeny were found outside the comparator range, with four of these levels having significantly greater variation in progeny than comparators.<sup>180</sup>

- ▲ In animals between 12 and 15 weeks old, chemistry values in progeny of clones showed indirect bilirubin/total bilirubin and bile acids had more outliers compared to non-clone progeny. FDA states that the progeny of clones "had low bilirubin. There is no known cause for low bilirubin. For this reason, this finding was considered not clinically relevant."<sup>181</sup> The sampling at this period also found that 12 clone progeny had elevated red blood counts, compared to just 2 comparators. FDA states, "The cause here is unknown but does not seem to indicate a health problem."<sup>182</sup>
- ▲ In analyzing meat from the progeny of clones, FDA notes that "a few nutrients did have differences in the variability and distribution of values between clone progeny and comparator swine."<sup>183</sup>

## GOATS

### FOOD SAFETY STUDIES ON GOAT CLONES AND PROGENY

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.<sup>184</sup> 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."<sup>185</sup>

The Agency's finding of safety thus relies entirely on health studies, which FDA reports selectively, omitting information on abnormal clones. FDA does acknowledge that "relatively few studies have been conducted with goat clones....,"<sup>186</sup> citing just four studies on survival of goat clones, none more recent than 2002.<sup>187</sup> FDA stated that its methodology for its risk assessment "explicitly excludes transgenic clones from the identification of hazards or risks experienced by "just clones" because of the inability to determine whether the transgenic event or cloning was causally associated with an adverse outcome." But the Agency found so few studies in goat cloning that it included studies on transgenic (GE) goats, and on both cloned and GE goats, in its review of the species.

Based on almost no health data, FDA concludes that cloned “Goats appear to grow and mature normally and produce normal progeny.”<sup>188</sup> In reviewing information about abnormalities in goat clones, the Agency states that “None of the studies reported cases of LOS [large offspring syndrome] or related perinatal clinical signs in goat clones.”<sup>189</sup> The Agency repeats this conclusion again in its summary on animal health, stating that “Unlike cattle and sheep, goat clones do not appear to develop LOS,”<sup>190</sup> and again in its conclusions on “food consumption risks from goat clones,” stating “all reports of health of the goat clones seem to indicate that they are normal and healthy.... goat clones appear to be healthy, and do not appear to be materially different from conventional goats.”<sup>191</sup> In its conclusion calling meat and milk from clones safe to eat, FDA states:

*The only anomaly noted* was that approximately half of the cohort of goats reported on by Keefer et al. (2001a) appeared to have poor suckling response immediately after birth... [emphasis added]

But FDA omits mention of abnormalities reported in another more recent study on goat clones, even though the Agency refers to this same study to support its finding that goat clones are normal. Twice FDA refers to a 2005 study by Behboodi et. al., noting that it is “the only study encountered to date that included data on hematology and clinical chemistry of goat clones,” and repeating (word for word) in both instances a summary of the studies findings of chemistry values in goat clones and comparators.<sup>192</sup>

But FDA fails to mention that the study encountered cloning problems similar to those seen in other species. The study concluded, “There was some evidence that as in other cloned species, there may be problems with placental development [in goat clones].”<sup>193</sup> In the study, six full-term pregnancies produced four live and three non-viable clones, reporting clinical signs indicative of LOS: “Anomalies at birth included enlarged umbilical stumps (one dead and two live fetuses) and minor tendon laxity in the limbs (three of four live animals); and minor generalized edema.”<sup>194</sup> FDA cited only four much earlier and smaller studies, some including transgenic goats, to support

its contention that goats do not exhibit these abnormalities. But only in the Appendix on “Transgenic Clones” does FDA mention the Behboodi findings,<sup>195</sup> which are otherwise completely ignored in the Agency’s conclusions on animal welfare and safety of food from goat clones.

Similarly, FDA cites four papers on survival in goat clones. Two of the four used genetically engineered (transgenic) goats, and all four studied just 21 total goats (8 of which were transgenic). The Agency fails to note that in these studies, the success rate of cloning was less than 8%, with two of the studies having success rates of less than 3%, about the same rate for clones of other species.<sup>196</sup> On the contrary, FDA later concludes, without citation, that “successful pregnancy outcome” in cloned goats “is very high”<sup>197</sup> and “Once clone embryos are transferred to surrogate dams and pregnancies are confirmed, the ‘success rate’ for live births is quite high.”<sup>198</sup> In fact, as one study noted, success rates in goat cloning even after pregnancy confirmation are highly variable, with some reports as low as 5%.<sup>199</sup>

Finally, FDA also misleadingly downplays a finding from one recent goat study that casts serious doubts about the Agency’s conclusions of the safety of progeny from all species of clones. In their study, Betts et al (2005) found that an abnormality (shortened telomere length) from cloning that is usually assumed to be erased in progeny were instead reproduced in progeny of goat clones.<sup>200</sup> This finding should have been noted and fully explored in the Agency’s analysis of all clone progeny, as it directly contradicts its major assumption for the safety of food from progeny. Instead, FDA merely states, “it is uncertain whether telomere length is a predictor of longevity.”<sup>201</sup>

## ANIMAL HEALTH: FOOD SAFETY RISKS AND ANIMAL WELFARE CONCERNS

### FOOD SAFETY AND ANIMAL WELFARE: GOAT CLONES BY DEVELOPMENTAL PERIOD

#### PREGNANCY AND PARTURITION

FDA cites just three papers on pregnancy in goat clones: all are from 2001 or earlier, two are on transgenic goats.<sup>202</sup> The Agency fails to note that cloning success rates in these studies were all below 8%.

For parturition, FDA's analysis consists of one sentence: "data on effects on surrogate dams are not currently available."<sup>203</sup> Yet in its conclusion, the Agency states, "there have been no adverse reports of pregnancy in surrogate goat does."<sup>204</sup>

#### *PERINATAL PERIOD*

FDA reports on one study that noted the death of twin goat clones at birth. Another study reported the death of three clones from respiratory illness: one at one day old, the others at one and three months. FDA states that "it is not possible to tell from this study whether the infections in these clones were potentiated by the [cloning] process."<sup>205</sup> FDA fails to note that in this study, the authors found that "the shape and distribution of the cotyledons [in recovered placenta] appeared slightly irregular."<sup>206</sup>

#### *JUVENILE DEVELOPMENT*

FDA discusses one study that stated goat clones were followed for a year, though no data was reported, other than "a few measurements" in an associated abstract.<sup>207</sup> They report on blood levels from the Behboodi study (see above), but fail to note that the authors found "the values for alkaline phosphatase, total proteins, and blood urea nitrogen (BUN) in the [cloned] animals were significantly different from the values detected in the control animals."<sup>208</sup>

#### *REPRODUCTIVE DEVELOPMENT*

FDA reports on just two studies, one of which used semen from just two clones. FDA notes that "The study did not mention whether there were any differences in

sperm quality or morphology between clones and controls."<sup>209</sup> The other study reported only that five clones "produced kids," with no data on age at puberty, number of services to conception, or details of the parturition and lactation.<sup>210</sup> FDA states that this study found a "100% success rate based on detectable pregnancy,"<sup>211</sup> but the Agency fails to paint the full picture. In fact, the authors found that

The pregnancy rate (defined as the number of pregnant recipients per total number of recipients) at 30 days of gestation was 21% (3/14) and 22% (2/9) for [the two clone groups], respectively. The overall pregnancy rate was 21.7% (5 of 23 recipients). Based on the number of offspring produced per number of embryos transferred, the cloning efficiency was 2.7%.<sup>212</sup>

In other words, the "100% success rate" reported by FDA was actually a 97.3% failure rate.

#### *POST-PUBERTAL PERIOD*

The FDA reports only that "No reports on aging and maturity in goat clones were identified."<sup>213</sup>

#### *PROGENY OF GOAT CLONES*

FDA cites two 2001 studies (one on transgenic goats) that found only that progeny of goat clones appeared healthy, reporting no data to support the conclusion.<sup>214</sup> The Agency also cites a third study finding that the progeny of goat clones had shorter telomere length than natural comparators (as discussed above).

## OTHER UNADDRESSED RISKS

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In its review, FDA states that its review assumes that “if clones were to pose food consumption risks, *the only mechanism* by which those risks could arise would be from inappropriate epigenetic reprogramming.”<sup>215</sup> From the outset, then, FDA’s review ignores several indirect risks to human health from cloning that scientists say should be part of the Agency’s assessment. None of the following health risks are reviewed in FDA’s analysis:

- ▲ *Bacterial contamination*: The NAS warned that pathogen shedding in veal and products from young clones could threaten food safety.<sup>216</sup> FDA notes several studies finding various infectious diseases in cloned animals,<sup>217</sup> but fails to evaluate the food safety risks that these pathogens could present.
- ▲ *Biodiversity*: Scientists say that by promoting genetically identical herds, cloning could put animals and humans at risk from disease epidemics. Reduced genetic diversity in cloned animal populations could create new reservoirs of infectious disease that pose threats to animal health and could spread to humans.<sup>218</sup>
- ▲ *Antibiotic-resistant disease*: The increased use of antibiotics in sickly clones could hasten the spread of antibiotic-resistant animal and/or human disease.

### LEGAL PETITION TO THE FDA ON FOOD FROM ANIMAL CLONES

In October 2006, the Center for Food Safety and a coalition of consumer, religious, animal welfare and other

groups filed a legal petition to FDA,<sup>219</sup> 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.

FDA has a long history of interpreting the definition of a “new drug” broadly, basing it on the functional claim intended from a new technology. Under the FFDCA, new drugs include “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”<sup>220</sup> Thus, for example, FDA is currently reviewing genetically engineered (GE) “fast growing” salmon under its “new animal drug” authority, because the GE fish is structurally and functionally affected by the technology.

Similarly, cloning companies claim that their technology will affect both the structure and function of the cloned animal, by producing animals with improved meat qualities or high-yielding dairy animals. Furthermore, cloning experts say that the cloning technology is the same in animals as it would be in humans, and FDA has already stated that any human cloning research would be regulated as a new drug by the agency under FFDCA, and would require submission of an “investigational new drug application.”<sup>221</sup> FDA offers no explanation as to why animal cloning should be exempted from the rigorous new drug review procedures that it requires for human cloning research.

## CONCLUSIONS AND RECOMMENDATIONS

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The Center for Food Safety legal petition to FDA calls on the Agency, pursuant to its statutory duty to protect the food supply, to regulate animal cloning as a “new animal drug.” The new animal drug process, which requires a rigorous pre-market review to determine efficacy and ensure food, animal, and environmental safety, will help to address the wide-spread concerns about and potential risks and impacts from animal cloning.

As part of its reviews, FDA should require multi-generational studies that include investigations of potential food safety threats from unexpected proteins or other metabolites produced by the cloning process.

Due to the uncertainty surrounding the long-term environmental impact of the introduction of cloned animals into the food-supply, FDA should prepare a full “environmental impact statement” for each new animal drug application based on the use of cloning.

Moreover, cloning animals for commercial livestock production will increase animal cruelty, because the process inherently involves needless suffering of surrogates and the deformed and sick offspring that often result from cloning. Animal cloning also is antithetical to some peoples’ moral and religious beliefs. Therefore, in addition to looking at the food safety issues, the Department of Health and Human Services should create an Advisory Committee on ethical issues in animal cloning. This

Advisory Committee should work with the FDA and provide expertise on the difficult ethical issues raised by animal cloning.

In sum, *FDA should 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.

# ENDNOTES

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- <sup>2</sup> 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>
- <sup>3</sup> 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](http://www.ucsusa.org/news/press_release/fda-scientists-pressured.html)
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- <sup>5</sup> NAS (2002), p. 75
- <sup>6</sup> FDA RA, p. 37
- <sup>7</sup> John Matheson, Center for Veterinary Medicine, U.S. Food and Drug Administration, quoted in "Animal Cloning and the Production of Food Products," Proceedings from a workshop sponsored by the Pew Initiative on Food and Biotechnology and the Center for Veterinary Medicine of the U.S. Food and Drug Administration, September 26, 2002, p. 31, online at <http://pewagbiotech.org/events/0924/proceedings2.pdf>
- <sup>8</sup> Randi Fabi, "FDA to Consider Ethical Concerns on Animal Cloning," Reuters, March 11, 2003
- <sup>9</sup> FDA, "Animal Cloning: FAQs About Cloning for Consumers," online at [http://www.fda.gov/cvm/CloningRA\\_FAQConsumers.htm](http://www.fda.gov/cvm/CloningRA_FAQConsumers.htm)
- <sup>10</sup> Ibid
- <sup>11</sup> 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
- <sup>12</sup> 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>)
- <sup>13</sup> FDA RA, p. 226
- <sup>14</sup> FDA RA, p. 163
- <sup>15</sup> FDA RA, p. 151-152
- <sup>16</sup> Ibid, p. F-28.
- <sup>17</sup> Archer, et. al. (2003) "Hierarchical Phenotypic and Epigenetic Variation in Cloned Swine." *BiolReprod*, 69, 430-436
- <sup>18</sup> FDA RA, p. 211
- <sup>19</sup> 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.
- <sup>20</sup> 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
- <sup>21</sup> NAS (2004), p. 222-228
- <sup>22</sup> Heyman, et. al. (2007) "Assessing the quality of products from cloned cattle: An integrative approach." *Theriogenology* 67:134-141
- <sup>23</sup> FDA RA, Appendix E, p. E-29
- <sup>24</sup> FDA RA, Appendix E, p. E-13
- <sup>25</sup> FDA RA, p. 104-107
- <sup>26</sup> Geir Tveit & Peter Sandøe (eds) (2005). p. 25
- <sup>27</sup> Rudolf Jaenisch (2004). "Human Cloning – The Science and Ethics of Nuclear Transplantation," 351 *NEW ENG. J.MED.* 2787
- <sup>28</sup> Larisa Rudenko and John C. Matheson (2007). "The US FDA and animal cloning: Risk and regulatory approach." *Theriogenology* 67, 198-206
- <sup>29</sup> FDA RA, p. 108
- <sup>30</sup> FDA RA, p. 115
- <sup>31</sup> FDA RA, p. 110-111
- <sup>32</sup> 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>
- <sup>33</sup> FDA RA, p. 149
- <sup>34</sup> FDA RA, p. 201-202 and Appendix E, p. E-6-8
- <sup>35</sup> See, for example, Pearson, Helen (2003), "Adult Clones in Sudden Death Shock," *Nature*, Scienceupdate, [On-line], URL: <http://www.nature.com/nsu/030825/030825-2.html>; Duncan Mansfield, "Cloned Cow Dies in Tennessee," Associated Press, June 5, 2001, online at <http://www.freerepublic.com/forum/a3b221ac957e0.htm>; Bio Tech Milestone at University Farm, [http://www.csuchico.edu/pub/inside/archive/01\\_03\\_29/01.newbiotech.html](http://www.csuchico.edu/pub/inside/archive/01_03_29/01.newbiotech.html) ; Melissa Trudinger, "Our first cloned sheep found dead," *Australian Biotechnology News*, 07/02/03.
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- <sup>38</sup> 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.
- <sup>39</sup> 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.
- <sup>40</sup> Since FDA found that food from sheep clones would not be suitable for food, we do not review here FDA's findings on sheep clones.
- <sup>41</sup> FDA RA, p. 248
- <sup>42</sup> FDA RA, p. 270
- <sup>43</sup> FDA RA, p. 258-270
- <sup>44</sup> FDA RA, p. 262
- <sup>45</sup> FDA RA, p. 258-261
- <sup>46</sup> FDA RA, p. 262
- <sup>47</sup> 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](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.
- <sup>48</sup> FDA RA, p. 265
- <sup>49</sup> FDA RA, p. 267-268
- <sup>50</sup> FDA RA, p. 270-274
- <sup>51</sup> FDA RA, p. 272
- <sup>52</sup> FDA RA, p. 276
- <sup>53</sup> FDA RA, p. 277-278
- <sup>54</sup> Laible, et. al. (2007) "Compositional analysis of dairy products derived from clones and cloned transgenic cattle." *Theriogenology* 67:166-177

- <sup>55</sup> Heyman, et. al. (2007) "Assessing the quality of products from cloned cattle: An integrative approach." *Theriogenology* 67:134–141
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- <sup>57</sup> FDA RA, p.180
- <sup>58</sup> Ibid
- <sup>59</sup> FDA RA, Appendix E, p. E-13
- <sup>60</sup> FDA RA, Appendix E, p. E-11-13
- <sup>61</sup> FDA RA, Appendix E, p. E-13
- <sup>62</sup> FDA RA, p. 110-111
- <sup>63</sup> FDA RA, p. 118-122
- <sup>64</sup> Panarace, et al (2007). "How healthy are clones and their progeny: 5 years of field experience." *Theriogenology* 67:142–151.
- <sup>65</sup> Ibid.
- <sup>66</sup> FDA RA, p. 115
- <sup>67</sup> FDA RA, p. 201
- <sup>68</sup> FDA RA, p. 108
- <sup>69</sup> FDA RA, p. 181
- <sup>70</sup> FDA RA, p. 109
- <sup>71</sup> FDA RA, p. 109
- <sup>72</sup> Ibid.
- <sup>73</sup> FDA RA, p. 187
- <sup>74</sup> FDA RA, p. 188
- <sup>75</sup> FDA RA, Appendix C, p.C-12-13
- <sup>76</sup> FDA RA, p. 111
- <sup>77</sup> FDA RA, p. 112
- <sup>78</sup> FDA RA, p. 111
- <sup>79</sup> FDA RA, p. 117
- <sup>80</sup> FDA RA, p. 116
- <sup>81</sup> FDA RA, p. 117
- <sup>82</sup> FDA RA, p. 104-107.
- <sup>83</sup> Cyagra's unpublished 2003 data in the chart shows a 78% survival rate, while in the one published study in 2003, survival was 71%.
- <sup>84</sup> Panarace, et al (2007). "How healthy are clones and their progeny: 5 years of field experience." *Theriogenology* 67:142–151.
- <sup>85</sup> FDA RA, p. 124
- <sup>86</sup> FDA RA, p. 124
- <sup>87</sup> FDA "Cloning 'Myths'", online at [http://www.fda.gov/cvm/CloningRA\\_Myths.htm](http://www.fda.gov/cvm/CloningRA_Myths.htm)
- <sup>88</sup> FDA RA, Appendix E, p. E-25
- <sup>89</sup> FDA RA, p.193
- <sup>90</sup> Chavatte-Palmer, et. al. (2002) "Clinical, Hormonal, and Hematologic Characteristics of Bovine Calves Derived from Nuclei from Somatic Cells." *Biology of Reproduction* 66, 1596-1603.
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- <sup>93</sup> Ibid
- <sup>94</sup> Wells, et. al. (2004). "The health of somatic cell cloned cattle and their offspring." *Cloning and Stem Cells*. Vol. 6, #2, pp. 101-110 [abstract at <http://md1.csa.com/partners/viewrecord.php?requester=gs&collection=ENV&recid=5997344&q=&uid=1040735&setcookie=yes>]
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- <sup>96</sup> Chavatte-Palmer, et. al (2004) "Health status of cloned cattle at different ages." *Cloning and Stem Cells*, 6(2), 94-100 (abstract)
- <sup>97</sup> Simon Collins, "Cloned animals dying at AgResearch," *New Zealand Herald*, November 14, 2002, online at [http://www.nzherald.co.nz/category/story.cfm?c\\_id=82&objectid=3004259](http://www.nzherald.co.nz/category/story.cfm?c_id=82&objectid=3004259)
- <sup>98</sup> FDA RA, p. 206-207
- <sup>99</sup> FDA RA, p. 207
- <sup>100</sup> FDA RA, Appendix E, p. E-29
- <sup>101</sup> FDA RA, Appendix E, p. E-29
- <sup>102</sup> FDA RA, p. 211
- <sup>103</sup> FDA RA, p. 140-141
- <sup>104</sup> FDA RA, p. 141
- <sup>105</sup> FDA RA, p. 142
- <sup>106</sup> FDA RA, p. 142
- <sup>107</sup> FDA RA, p. 144-145
- <sup>108</sup> FDA RA, p. 143
- <sup>109</sup> FDA RA, p. 144-145
- <sup>110</sup> FDA RA, p.145-147
- <sup>111</sup> FDA RA, p. 148-149
- <sup>112</sup> FDA RA, p. 149-150; Appendix E, p. E-30-31
- <sup>113</sup> FDA RA, Appendix E, p. E-33
- <sup>114</sup> FDA RA, Appendix E, p. E-7
- <sup>115</sup> Ibid. p. E-8
- <sup>116</sup> FDA RA, Appendix E, p. E-6
- <sup>117</sup> FDA RA, p. 201-202
- <sup>118</sup> FDA RA, p. 201-202 and Appendix E, p. E-6-8
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- <sup>136</sup> FDA RA, p. 240
- <sup>137</sup> FDA RA, Appendix F, p. F-47.
- <sup>138</sup> FDA RA, p. 161
- <sup>139</sup> FDA RA, p. 238
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- <sup>216</sup> NAS (2002) p. 65.
- <sup>217</sup> FDA RA p. 299
- <sup>218</sup> NAS (2002), p. 48–9
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- <sup>221</sup> Testimony of Dr. Kathryn C. Zoon, Director, Center for Biologics Evaluation and Research, Food and Drug Administration, to the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, March 28, 2001, online at <http://energy-commerce.house.gov/reparchives/107/hearings/03282001Hearing141/Zoon205.htm>