



National Milk Producers Federation

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May 3, 2007

Docket No. 2003N-0573
Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: Docket No. 2003N-0573 Draft Animal Cloning Risk Assessment; Proposed Risk Management Plan; Draft Guidance for Industry; Notice of Availability

To Whom It May Concern:

The National Milk Producers Federation (NMPF) is submitting the following comments to the Food and Drug Administration's (FDA) Notice of Availability entitled Draft Animal Cloning Risk Assessment; Proposed Risk Management Plan; Draft Guidance for Industry; Docket Number 2003N-0573. The National Milk Producers Federation, based in Arlington, VA, develops and carries out policies that advance the well being of dairy producers and the cooperatives they own. The members of NMPF's 32 cooperatives produce the majority of the U.S. milk supply, making NMPF the voice of nearly 50,000 dairy producers on Capitol Hill and with government agencies.

Dairy producers have routinely been at the fore-front of technological innovation in assisted reproductive technologies (ART). Artificial insemination was first commercialized in the dairy industry over 60 years ago and is used routinely on dairy farms today. Although not as common as artificial insemination, *In vitro* fertilization and embryo transfer have nearly three decades of proven efficacy allowing dairy producers to select their best cows to serve as the foundation for future generations of dairy cattle. Cloning has been conducted on a limited basis in the dairy industry for twenty years, initially in the form of embryo splitting which results in two or more identical offspring from the same zygote. Somatic cell nuclear transfer (SCNT) is a cloning technique which produces a clone from an adult animal. Due to cost, SCNT is not expected to be widely adopted in the dairy industry. A limited number of SCNT dairy animals are expected to be produced each year – including dairy cows and bulls with superior genetics and animals intended for exhibition in type evaluation contests (such as State Fairs and the World Dairy Expo).

Agri-Mark, Inc.
Arkansas Dairy Cooperative Association
Associated Milk Producers, Inc.
Cass-Clay Creamery, Inc.
Continental Dairy Products, Inc.
Cooperative Milk Producers Assn.
Dairy Farmers of America, Inc.
Dairymen's Marketing Cooperative, Inc.
Dairylea Cooperative Inc.
Ellsworth Cooperative Creamery
Farmers Cooperative Creamery
First District Association
Foremost Farms USA
Humboldt Creamery
Just Jersey Cooperative, Inc.
Land O'Lakes, Inc.
Lone Star Milk Producers, Inc.
Manitowoc Milk Producers Coop.
MD & VA Milk Producers Cooperative Association, Inc.
Michigan Milk Producers Assn.
Mid-West Dairymen's Company
Northwest Dairy Association
Prairie Farms Dairy, Inc.
St. Albans Cooperative Creamery, Inc.
Scioto County Co-op Milk Producers' Assn.
Select Milk Producers, Inc.
Southeast Milk, Inc.
Swiss Valley Farms, Co.
Tillamook County Creamery Assn.
United Dairymen of Arizona
Upstate Niagara Cooperative, Inc.
Zia Milk Producers

Jerry Kozak, President/Chief Executive Officer

Charles Beckendorf, Chairman

www.nmpf.org

The present debate on cloning and FDA's notice of availability of documents refers specifically to SCNT. NMPF has carefully reviewed the documents FDA has requested comment on and will provide comments in the following areas: (1) the Draft Animal Cloning Risk Assessment (Risk Assessment); (2) the Draft Risk Management Plan (Risk Management Plan); (3) Labeling Guidance for Industry (Guidance for Industry); (4) interagency consultation; and (5) market impacts.

DRAFT RISK ASSESSMENT

Many peer-reviewed studies have been published on livestock cloning. Indeed, the Risk Assessment is exhaustive in its analysis of risks associated with milk and meat products from cloned animals and their progeny. In an earlier risk assessment, the French Food Safety Agency (AFSSA) noted that reviewed research "did not reveal any difference between the animals [clones] tested and controls [conventionally bred animals]."¹ For milk from cloned cattle, AFSSA found "No significant differences have been observed relative to the following parameters: total solid quantity, minerals, proteins, fats, lactose, pH, SCC (somatic cell counts), ADV (acid degree value). A more detailed examination has also revealed that the proportion of the various milk proteins (caseins and lactoserum proteins), along with the relative concentration of the various fatty acids, is identical in cows obtained by cloning and in control animals. The first experiments conducted with the progeny of clones confirm these conclusions."²

FDA's conclusions in the Risk Assessment are similar to those from AFSSA. In reviewing the Risk Assessment and the associated scientific evidence upon which it is based, NMPF conclude that milk and meat products from cloned animals and their progeny are indistinguishable from conventionally bred animals. Specifically, we conclude:

- Milk composition is not different between cloned cows and their conventional counterparts because of cloning, rather any differences observed are due to genetic differences between animals and feeding regime, and are within normal ranges for dairy cattle.
- Meat composition is not different between cloned cows and their conventional counterparts because of cloning, rather any differences observed are due to genetic differences between animals and feeding regime, and are within normal ranges for dairy cattle.
- Food safety is not different for milk and meat between cloned cows and their conventional counterparts because of cloning, and food safety parameters are within normal ranges for cattle.
- Animal health risks for cloned cattle are the same risks that conventionally bred cattle face, although at a higher frequency particularly for surrogate dams and during the perinatal period.

¹ French Food Safety Agency (AFSSA). September 2005.

² IBID

- Progeny of cloned cattle produced by conventional breeding methods have the same food safety and animal health risks as progeny of non-cloned cattle produced by conventional breeding methods.

For the Risk Assessment, FDA reviewed available literature through early 2006 at which point new literature could not be reviewed due to time requirements for publication.³ During the public comment period, FDA asked for submission of data and other relevant information which will be thoroughly reviewed so any necessary revisions can be made to the Risk Assessment. NMPF has identified many scientific peer-reviewed articles published after early 2006 on SCNT cloning. Additionally for a few scientific peer-reviewed articles published prior to early 2006, it is unclear if FDA analyzed these articles as they have not been cited in the Risk Assessment. The scientific peer-reviewed articles on livestock cloning listed in **APPENDIX A** have not been included in FDA's analysis for the Risk Assessment. NMPF recommends FDA conduct a thorough analysis of these articles prior to finalizing the Risk Assessment.

FDA also reviewed considerable volumes of data from cloning technology providers in the Risk Analysis. As with scientific peer-reviewed literature, FDA stopped the collection of additional data from cloning technology providers in early 2006 at which point new data could not be reviewed due to time requirements for publication. NMPF recommends FDA solicit any new data that cloning technology providers may have generated since early 2006 for thorough analysis and inclusion in the Risk Assessment.

DRAFT RISK MANAGEMENT PLAN

Based on analysis provided in the Risk Assessment, NMPF concurs with FDA that food and feed derived from SCNT cloned animals do not pose any unique risks compared to conventionally bred animals. Additionally based on analysis provided in the Risk Assessment, NMPF concurs with FDA that foods derived from progeny (resulting from conventionally breeding – sexual reproduction) of SCNT cloned animals are suitable to enter the marketplace under the same controls as applied to any animal that is the product of sexual reproduction.

NMPF strongly supports continued monitoring of the *State of Science* of cloning including new data, changes in cloning techniques and technology, and the increasing knowledge base on the biology of epigenetic mechanisms governing gene expression and their role in nuclear transfer. An appropriate starting point for this continued monitoring is a thorough review of all new scientific peer-reviewed literature (listed in **APPENDIX A**) and additional data from cloning technology providers that has occurred since FDA stopped reviewing data in early 2006.

Standards of Care for Animals Involved in Cloning – As noted in earlier comments on the Risk Assessment animal health risks for cloned cattle are the same risks that

³ FDA-CVM. 2006. Pp. iv in *Animal Cloning: A Draft Risk Assessment*. December 28.

conventionally bred cattle face, but some of these animal health risks occur at a higher frequency particularly for surrogate dams and during the perinatal period. NMPF believes it is appropriate to develop Standards of Care for Animals Involved in Cloning (Standards of Care) for SCNT clones and their surrogate dams. NMPF encourages FDA to engage cloning technology providers, scientific organizations (such as the International Embryo Transfer Society), and veterinarian organizations (such as the American Association of Bovine Practitioners) in the development of the Standards of Care.

Alternatively, the Animal Welfare Act⁴ requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, transported commercially, or exhibited to the public. NMPF is unsure whether the Animal Welfare Act would apply to SCNT clones and their surrogate dams as they may be exempt as warm-blooded animals used for food, fiber, or other agricultural purposes. If SCNT clones and their surrogate dams are subject to the Animal Welfare Act, NMPF asserts this would only cover the production of the SCNT clone through the perinatal period at the cloning technology provider location. Once transferred to a commercial farm, the SCNT clone would no longer be subject to the Animal Welfare Act due to the aforementioned exemptions.

Either FDA developed Standards of Care or any applicable Animal Welfare Act requirements should only apply to the SCNT clone and their surrogate dam through the perinatal period and **not** through the entire life cycle of the SCNT clone. Once beyond the perinatal period and transferred to a commercial farm, the SCNT clone would be subject to the same animal care standards that conventionally bred dairy cattle are subject to. The dairy industry has developed voluntary guidelines as Standards of Care for dairy animals. For example, the Caring for Dairy Animals Technical Reference Guide⁵ describes husbandry practices that foster the well-being of dairy animals explaining why the animals' comfort, safety, and good health are the reason for designing the animals' living environment in a particular way or using certain animal handling and management practices.

LABELING GUIDANCE FOR INDUSTRY

Mandatory Labeling – NMPF opposes labeling which differentiates between milk and meat from cloned animals and milk and meat from conventionally-bred animals because the products are indistinguishable (see **DRAFT RISK ASSESSMENT**). Because FDA possess significant scientific evidence demonstrating the safety of milk from SCNT clones and their progeny, FDA can soundly determine that there is no special requirement to label milk from SCNT clones or their progeny. FDA reached a similar conclusion concerning rbST whereby there could be no special requirement to label

⁴ Administered by the Animal and Plant Health Inspection Service – 9 CFR 1-167.

⁵ Carlson, K.R., C. Johnston, and D. Bals. 2004. Caring for dairy animals technical reference guide. Agri-Education, Inc.; Stratford, IA.

milk from cows administered rbST.⁶ In the case of *IDFA v. Amestoy*,⁷ the court found that consumer interest alone could not justify mandatory label disclosures when there is no human safety or health concerns associated with food products derived from cows administered rBST. NMPF contends this ruling merits no mandatory labeling of milk and meat from cloned animals and their progeny and because they are indistinguishable from milk and meat from conventionally-bred animals.

Negative Labeling Claims – While negative (or absence) claims are allowed by FDA on some products, the statements must not be false or misleading. Because milk and meat products from cloned animals and their progeny are indistinguishable from those of conventionally-bred animals any negative claim which leads a consumer to believe milk and meat from cloned animals or their progeny are different will be false and misleading. NMPF has great concern that such statements may be allowed in the marketplace with the intention to lead consumers to the belief that milk and meat products from cloned animals and their progeny are different when they are not and recommends that FDA pursue vigorous enforcement of labeling requirements. NMPF opposes the allowance of negative label claims because of the propensity for them to be false or misleading.

While NMPF believes any negative label claims will be deceptive to consumers, FDA labeling guidance for rbST⁸ set a precedent in allowing negative label claims. If negative labels claims are to be allowed (which NMPF opposes) any negative label claim should be accompanied by inclusion of proper context about the lack of differences in milk derived from cloned and non-cloned cows.

FDA-issued industry guidance on voluntary labeling of milk and milk products will be necessary if negative label claims are allowed. In **APPENDIX B**, NMPF proposes **Guidance on the Voluntary Labeling of Milk and Milk Products From Cows That Are Not Derived From Somatic Cell Nuclear Transfer (Cloning)** which FDA could use as the basis for such industry guidance.

Federal Preemption – NMPF is aware of legislation in at least eight states that would prescribe mandatory labeling for food products derived from cloned animals. As previously stated, NMPF opposes mandatory labeling which differentiates between milk and meat from cloned animals and milk and meat from conventionally-bred animals because the products are indistinguishable. This opposition includes efforts at the state or local level to require mandatory labeling.

The Nutrition Labeling and Education Act (NLEA) established most Federal food labeling requirements as national uniform standards through Federal preemption of state requirements. Under NLEA, no state can directly or indirectly establish any requirement that is not identical to a Federal requirement under the provisions of the Food Drug and Cosmetic Act which is given preemptive effect. Any product

⁶ 59 FR 6279.

⁷ 92 F.3d 67 (2d Cir. 1996).

⁸ 59 FR 6279.

introduced into interstate commerce is subject to FDA regulations. In practice courts have interpreted the scope of interstate commerce broadly to include a products ingredients and packaging materials, so NMPF believe virtually all milk and milk products would be subject to Federal preemption. NMPF recommends that FDA actively enforce Federal preemption for food labeling requirements to prohibit any mandatory labeling requirements by states for milk and milk products involved in interstate commerce.

Organic Standards – The National Organics Standards Board is considering precluding cloning from the National Organic Program.⁹ NMPF believes that the National Organic Program is the preferred alternative for consumers to be able to purchase milk and milk products derived from non-cloned animals rather than a system of misleading negative label claims.

NMPF believes that cloning (and thereby food products derived from clones) is already excluded by the National Organic Program. Under Excluded Methods¹⁰ a “variety of methods used to genetically modify organisms or influence their growth and development by means that are not possible under natural conditions or processes and are not considered compatible with organic production. Such methods include **cell fusion** (emphasis added), microencapsulation and macroencapsulation, and recombinant DNA technology (including gene deletion, gene doubling, introducing a foreign gene, and changing the positions of genes when achieved by recombinant DNA technology).” During somatic cell nuclear transfer, DNA from an adult cell is fused (cell fusion) with an enucleated egg *in vitro* to produce a clone embryo. Clearly somatic cell nuclear transfer cloning which is a result of cell fusion is an Excluded Method in the National Organic Program.

INTERAGENCY CONSULTATION

Under Executive Order 12866 *Regulatory Planning and Review*,¹¹ an agency must determine whether a regulatory action¹² is “significant” and therefore subject to Office of Management and Budget (OMB) review and the requirements of the Executive Order. The Executive Order defines a “significant regulatory action” as one that is likely to result in a rule that may: (1) Have an annual effect on the economy of \$100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or Tribal governments or communities; (2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) Materially alter the budgetary impact of entitlements, grants, user fees, or

⁹ 72 FR 10971-10973.

¹⁰ 7 CFR § 205.2

¹¹ Executive Order 12866 of September 30, 1993, as amended by E.O. 13258 of February 26, 2002 and E.O. 13422 of January 18, 2007.

¹² FDA’s Risk Assessment leading to a determination that cloning technology does not need to be regulated under the Food Drug and Cosmetic Act is itself, a regulatory action which subjects any action by FDA on cloning technology to requirements of Executive Order 12866.

loan programs or the rights and obligations of recipients thereof; or (4) Raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order.

NMPF has determined that the Risk Assessment, Risk Management Plan, and Guidance for Industry are a "significant regulatory action" under the terms of Executive Order 12866. Specifically, NMPF believes that the annual effect on the dairy sector of the economy to be greater than \$100 million annually (detailed in **MARKET IMPACTS**). Prior to this action being finalized NMPF recommends that it be submitted to OMB for review with any changes made in response to OMB suggestions or recommendations documented in the public record. During OMB review, NMPF recommends that the U.S. Department of Agriculture and the Office of the U.S. Trade Representative be included in interagency consultation (detailed in **MARKET IMPACTS**).

MARKET IMPACTS

International Markets – Exports have become an important outlet for U.S. dairy production. In 2006, U.S. dairy exports reached a record of nearly \$1.9 billion and totaled more than 2 billion pounds of milk solids. This record volume represented 9.3 percent of total U.S. milk solids production, an all-time high and more than doubles the percentage of just 10 years ago.

The U.S. Dairy Export Council (USDEC)¹³ gathered extensive information from its exporting and processing members in order to assess the prospective commercial impact of commercialized cloning on milk and milk product sales from the U.S. in the international marketplace. Though membership opinion was not entirely uniform, a clear concern was evident over the commercial impact that might come about if milk from cloned animals is permitted into commercial channels.

USDEC members felt that cheese exports (\$245 million in 2006), would be severely affected. Seventy percent of the respondents felt export sales could drop by at least 10 to 24% (\$25 - \$59 million), while two of the larger exporters thought sales could drop by 25% or more. In limited responses for non-fat dry milk exports (\$589 million in 2006), exporters believed export sales could drop between one-quarter and one-half (\$147 - \$295 million). For whey protein concentrate exports (\$105 million in 2006), one-third of the respondents suggested export sales could drop by 25 to 49% (\$26 - \$53 million). This potential economic impact to the dairy sector is greater than the \$100 million trigger level for OMB review under Executive Order 12866 (see **INTERAGENCY CONSULTATION**).

¹³ USDEC is a non-profit, independent membership organization that represents the export trade interests of U.S. milk producers, proprietary processors, dairy cooperatives, and export traders. The Council's mission is to increase the volume and value of U.S. dairy product exports.

A mitigating factor on international markets identified by USDEC is policies that might be adopted by national regulatory authorities in other countries regarding products from cloned animals. For example, international concerns might diminish if suppliers of competitive products like New Zealand or Australia permitted the commercial sales of such products. A similar beneficial effect might occur if large buyers, such as Japan, adopted a similar policy as the one presented by the FDA. Conversely, the absence of, or adoption of unfavorable rulings, could aggravate the effect on U.S. dairy exports.

International efforts are just beginning to address products from cloned animals in the marketplace. The European Food Safety Authority has been tasked to “assess the possible implications of cloning for food safety, animal health, animal welfare and environment in the EU” with a ruling due in six months.¹⁴ Food Standards Australia New Zealand is currently assessing the food safety evidence of cloned animal products and will provide its analysis to the Australian Government for consideration.¹⁵ At a minimum, meaningful international dialogue, cooperation and coordination directed towards achieving a smooth pathway to global introduction would go a long ways to resolve any possible disputes in the international marketplace and may prevent long and costly trade challenges from reaching the World Trade Organization. NMPF recommends that FDA decision-making on cloned animal products entering commerce be harmonized with international efforts to ensure international market access for U.S. dairy products is not disrupted.

Domestic Markets – While consumer acceptance of new technology is not a mandatory consideration under FDA’s regulatory purview, FDA in the past has recognized the importance of ensuring consumer confidence in new technologies affecting food production.¹⁶ With the impending introduction of rbST, OMB concluded that the need for credible nutrition information and education on rBST is substantial, and could likely reduce consumer concerns about rbST.¹⁷ NMPF believes that the same principles to ensure consumer confidence apply to products derived from cloned animals. Strong enforcement to prevent misleading and untruthful labeling is one avenue to maintain consumer confidence (see **LABELING GUIDANCE FOR INDUSTRY**). A negative consumer reaction to milk and milk products due to lack of confidence in safety of cloning will have a decisive impact on all segments of the dairy industry. NMPF encourages FDA to take all steps necessary to prevent a negative consumer reaction.

¹⁴ Ennis, D. 2007. EU agency asked to rule on cloned meat and milk. Scientific American. March 8th (<http://www.sciam.com/article.cfm?chanID=sa003&articleID=5DE310FD9365CD111D778791085B1EB3>). Accessed March 20, 2007.

¹⁵ Food Standards Australia New Zealand. 2007. Food derived from cloned animals and their offspring. (<http://www.foodstandards.gov.au/newsroom/factsheets/factsheets2007/foodderivedfromclone3452.cfm>). Accessed March 20, 2007.

¹⁶ Executive Branch of the Federal Government (USA). 1994. Use of Bovine Somatotropin (BST) in the United States: its potential effects. Office of the Management of the Budget, Washington, DC.

¹⁷ IBID.

Economic Impacts – The impact of the Risk Assessment on U.S. dairy industry may be negative as evinced by the potential impacts on U.S. Dairy exports. Similarly, there will be domestic market implications based upon consumer confidence in the Risk Assessment. Executive Order 12866 reads in part, “In deciding whether and how to regulate, agencies should assess all costs and benefits of available regulatory alternatives, including the alternative of not regulating. Costs and benefits shall be understood to include both quantifiable measures (to the fullest extent that these can be usefully estimated) and qualitative measures of costs and benefits that are difficult to quantify, but nevertheless essential to consider.”¹⁸ NMPF recommends that FDA perform a complete economic impact analysis based upon the Risk Assessment to meet obligations under Executive Order 12866.

CONCLUSIONS

In reviewing the Risk Assessment and the associated scientific evidence upon which it is based, NMPF concludes that milk and meat products from cloned animals and their progeny are indistinguishable from conventionally bred animals. Food and feed derived from SCNT cloned animals do not pose any unique risks compared to conventionally bred animals. NMPF has identified many scientific peer-reviewed articles published on livestock cloning (see **APPENDIX A**) that have not been included in FDA’s analysis for the Risk Assessment. NMPF recommends FDA include a thorough analysis of these articles prior to finalization of the Risk Assessment.

NMPF supports continued monitoring of the *State of Science* of cloning including new data, changes in cloning techniques and technology, and the increasing knowledge base on the biology of epigenetic mechanisms governing gene expression and their role in nuclear transfer. Due to increase animal health risks for cloned cattle and their surrogate dams particularly during the perinatal period, NMPF believes it is appropriate to develop *Standards of Care for Animals Involved in Cloning*. NMPF encourages FDA to engage cloning technology providers, scientific organizations, and veterinarian organizations in the development of the Standards of Care.

Because FDA possess significant scientific evidence demonstrating the safety of milk from SCNT clones and their progeny, NMPF opposes labeling which differentiates between milk and meat from cloned animals and milk and meat from conventionally-bred animals. NMPF has great concern that negative label claims may be allowed in the marketplace with the intention to mislead consumers to the belief that milk and meat products from cloned animals and their progeny are different from those of conventionally bred animals and recommends that FDA pursue vigorous enforcement of labeling requirements. NMPF opposes the allowance of negative label claims because of the propensity for them to be false or misleading; however if negative label claims are allowed, NMPF proposes that FDA issue industry guidance on voluntary

¹⁸ Executive Order 12866 of September 30, 1993, as amended by E.O. 13258 of February 26, 2002 and E.O. 13422 of January 18, 2007.

labeling of dairy products from cloned cows to ensure any statements are not false and misleading (**APPENDIX B**).

Due to potential trade implications (estimated in excess of \$100 million annually), a meaningful international dialogue directed towards achieving a smooth pathway to global introduction would go a long ways to resolve any possible disputes in the international marketplace and may prevent long and costly trade challenges from reaching the World Trade Organization. NMPF recommends that FDA decision-making on cloned animal products entering commerce be harmonized with international efforts to ensure international market access for U.S. dairy products is not disrupted. Similarly, there will be domestic market implications based upon consumer confidence in the Risk Assessment. NMPF recommends that FDA perform a complete economic impact analysis based upon the Risk Assessment to meet obligations under Executive Order 12866.

Thank you for the opportunity to submit these comments. Please contact NMPF if you have any questions or require any clarification of these comments.

Sincerely,

A handwritten signature in purple ink that reads "Jamie S. Jonker". The signature is written in a cursive style with a large initial "J" and "S".

Jamie S. Jonker, Ph.D.
Director, Regulatory Affairs
National Milk Producers Federation

APPENDIX A

These scientific peer-reviewed articles on livestock cloning listed below have not been included in FDA's analysis for the Risk Assessment. NMPF recommends FDA include a thorough analysis of these in the Risk Assessment.

Akagi, S., N. Adachi, K. Matsukawa, M. Kubo, and S. Takahashi 2003. Developmental potential of bovine nuclear transfer embryos and postnatal survival rate of cloned calves produced by two different timings of fusion and activation. *Mol Reprod Dev.* 66(3):264-72.

Allen, J.F., and C.A. Allen . 1999. A mitochondrial model for premature ageing of somatically cloned mammals. *IUBMB Life.* 48(4):369-72.

Apimeteetumrong, M., A. Thuangsanthia, N. Leingcharoen, V. Yiengvisavakul, A. Harintharanon, A. Kunavongkrit, J. Sumretprasong, X. Vignon, and M. Techakumphu. 2004. The effect of activation protocols on the development of cloned goat embryos. *J Vet Med Sci.* 66(12):1529-34.

Arnold, D.R., V. Bordignon, R. Lefebvre, B.D. Murphy, and L.C. Smith. 2006. Somatic cell nuclear transfer alters peri-implantation trophoblast differentiation in bovine embryos. *Reproduction.* 132(2):279-90.

Aston, K.I., G.P. Li, B.A. Hicks, B.R. Sessions, B.J. Pate, D. Hammon, T.D. Bunch, and K.L. White. 2006. The developmental competence of bovine nuclear transfer embryos derived from cow versus heifer cytoplasts. *Anim Reprod Sci.* 95(3-4):234-43.

Aston, K.I., G.P. Li, B.A. Hicks, B.R. Sessions, B.J. Pate, D. Hammon, T.D. Bunch, and K.L. White. 2006. Effect of the time interval between fusion and activation on nuclear state and development in vitro and in vivo of bovine somatic cell nuclear transfer embryos. *Reproduction.* 131(1):45-51.

Batchelder, C.A., K.A. Hoffert, M. Bertolini, A.L. Moyer, J.B. Mason, S.G. Petkov, T.R. Famula, and G.B. Anderson. 2005. Effect of the nuclear-donor cell lineage, type, and cell donor on development of somatic cell nuclear transfer embryos in cattle. *Cloning Stem Cells.* 7(4):238-54.

Betthausen, J.M., M. Pfister-Genskow, P.J. Xu H, Golueke, J.C. Lacson, R.W. Koppang, C. Myers, B. Liu, I. Hoeschele, K.J. Eilertsen, G.H. Leno. 2006. Nucleoplasmin facilitates reprogramming and in vivo development of bovine nuclear transfer embryos. *Mol Reprod Dev.* 73(8):977-86.

Beyhan, Z., E.J. Forsberg, K.J. Eilertsen, M. Kent-First, and N.L. First. 2007. Gene expression in bovine nuclear transfer embryos in relation to donor cell efficiency in producing live offspring. *Mol Reprod Dev.* 74(1):18-27.

Bhak, J.S., S.L. Lee, S.A. Ock, B. Mohana Kumar, S.Y. Choe, and G.J. Rho. 2006. Developmental rate and ploidy of embryos produced by nuclear transfer with different activation treatments in cattle. *Anim Reprod Sci.* 92(1-2):37-49.

Bhojwani, S., W. Tomek, L. Jonas, F. Becker, H. Alm, H. Torner, W. Kanitz, and R. Poehland. 2006. Itrastructural analysis reveals striking differences of intercellular contact lengths in bovine embryos produced in vivo, in vitro and by somatic cell nuclear transfer. *Mol Reprod Dev.* *In press.*

Bhojwani, S., G. Vajta, H. Callesen, K. Roschlau, A. Kuwer, F. Becker, H. Alm, H. Torner, W. Kanitz, and R. Poehland. 2005. Developmental competence of HMC(TM) derived bovine cloned embryos obtained from somatic cell nuclear transfer of adult fibroblasts and granulosa cells. *J Reprod Dev.* 51(4):465-75.

Booth, P.J., S.J. Tan, P. Holm, and H. Callesen. 2001. Application of the zona-free manipulation technique to porcine somatic nuclear transfer. *Cloning Stem Cells.* 3(4):191-7.

Booth, P.J., S.J. Tan, R. Reipurth, P. Holm, and H. Callesen. 2001. Simplification of bovine somatic cell nuclear transfer by application of a zona-free manipulation technique. *Cloning Stem Cells.* 3(3):139-50.

Bordignon, V., and L.C. Smith. 2006. Telophase-stage host ooplasm support complete reprogramming of roscovitine-treated somatic cell nuclei in cattle. *Cloning Stem Cells.* 8(4):305-17.

Bousquet, D., and P. Blondin. 2004. Potential uses of cloning in breeding schemes: dairy cattle. *Cloning Stem Cells.* 6(2):190-7. *Review.*

Bruggerhoff, K., V. Zakhartchenko, H. Wenigerkind, H.D. Reichenbach, K. Prella, W. Scherthaner, R. Alberio, H. Kuchenhoff, M. Stojkovic, G. Brem, S. Hiendleder, and E. Wolf. 2002. Bovine somatic cell nuclear transfer using recipient oocytes recovered by ovum pick-up: effect of maternal lineage of oocyte donors. *Biol Reprod.* 66(2):367-73.

Chavatte-Palmer, P., N. de Sousa, P. Laigre, S. Camous, A.A. Ponter, J. F. Beckers, and Y. Heyman. 2006. Ultrasound fetal measurements and pregnancy associated glycoprotein secretion in early pregnancy in cattle recipients carrying somatic clones. *Theriogenology.* 66(4):829-840.

Chen, D.Y., M. X. Jiang, Z.J. Zhao, H.L. Wang, Q. Y. Sun, L.S. Zhang, R.C. Li, H.H. Cao, Q.J. Zhang, and D.L. Ma. 2007. Cloning of Asian yellow goat (*C. hircus*) by somatic cell nuclear transfer: telophase enucleation combined with whole cell intracytoplasmic injection. *Mol Reprod Dev.* 74(1):28-34.

Chen, J.Q., Y. Pan, J.Y. Zhao, Y.Y. Cao, X.J. Xu, R.J. Zhou, S.L. Zhang, S.Y. Wang, and G.X. Cheng. 2002. Study on the cloning goat by cross-breed somatic cell nuclear transfer [*Chinese*]. *Shi Yan Sheng Wu Xue Bao*. 35(4):278-82.

Cheng, Y., Y.G. Wang, J.P. Luo, Y. Shen, Y.F. Yang, H.M. Ju, X.G. Zou, S.F. Xu, W.D. Lao, and M. Du. 2002. Cloned goats produced from the somatic cells of an adult transgenic goat [*Chinese*]. *Sheng Wu Gong Cheng Xue Bao*. 18(1):79-83.

Cho, J., M.M. Bhuiyan, S. Shin, E. Park, G. Jang, S. Kang, B. Lee, and W. Hwang. 2004. Development potential of transgenic somatic cell nuclear transfer embryos according to various factors of donor cell. *J Vet Med Sci*. 66(12):1567-73.

Constant, F., M. Guillomot, Y. Heyman, X. Vignon, P. Laigre, J.L. Servely, J.P. Renard, and P. Chavatte-Palmer. 2006. Large offspring or large placenta syndrome? Morphometric analysis of late gestation bovine placentomes from somatic nuclear transfer pregnancies complicated by hydrallantois. *Biol Reprod*. 75(1):122-30.

Dai, Y., L. Wang, H. Wang, Y. Liu, N. Li, Q. Lyu, D.L. Keefe, D.F. Albertini, and L. Liu. 2006. Fate of centrosomes following somatic cell nuclear transfer (SCNT) in bovine oocytes. *Reproduction*. 131(6):1051-61.

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APPENDIX B

Guidance on the Voluntary Labeling of Milk and Milk Products From Cows That Are Not Derived From Somatic Cell Nuclear Transfer (Cloning)

Appropriate Labeling Statements

At the Federal level, statements about cloning in the labeling of food shipped in interstate commerce would be reviewed under sections 403(a) and 201(n) of the Act. Under section 403(a) of the Act, a food is misbranded if statements on its label or in its labeling are false or misleading in any particular. Under section 201(n), both the presence and the absence of information are relevant to whether labeling is misleading. That is, labeling may be misleading if it fails to disclose facts that are material in light of representations made about a product or facts that are material with respect to the consequences that may result from use of the product. Thus, certain labeling statements about cloning may be misleading unless they are accompanied by additional information. This guidance is based on the use of the false or misleading standard in the Federal law, which is incorporated in many States' food and drug laws. States may also have additional authorities that are relevant in regulating such claims.

FDA is concerned that the term “clone free” or associated derivations may imply a compositional difference between milk from cloned cows rather than a difference in the way the milk is produced. Instead, the concept would better be formulated as “from cows not produced by somatic cell nuclear transfer (cloning)” or in other similar ways. However, even such a statement, which asserts that cloning has not been used in the production of the subject milk, has the potential to be misunderstood by consumers. Without proper context, such statements could be misleading. Such unqualified statements may imply that milk from non-cloned cows is safer or of higher quality than milk from cloned cows. Such an implication would be false and misleading.

FDA believes such misleading implications could best be avoided by the use of accompanying information that puts the statement in a proper context. Proper context could be achieved in a number of different ways. For example, accompanying the statement “from cows not produced by somatic cell nuclear transfer (cloning)” with the statement that “No difference has been shown between milk derived from somatic cell nuclear transfer clone cows and non-clone cows” would put the claim in proper context. Proper context could also be achieved by conveying the firm's reasons (other than safety or quality) for choosing not to use milk from cloned cows, as long as the label is truthful and not misleading.

States should evaluate any labeling statement about cloning in the context of the complete label and all labeling for the product, as well as of any advertising for the product. Available data on consumers' perceptions of the label statements could also be used to determine whether a statement is misleading.

Substantiation of Labeling Claims

There is no way to differentiate analytically between milk produced by cloned cows from non-cloned cows, nor are there any measurable compositional differences between milk from cloned cows and by non-cloned cows. Therefore, to ensure that claims that milk comes from non-cloned cows are valid, States could require that firms that use such claims establish a plan and maintain records to substantiate the claims, and make those records available for inspection by regulatory officials. The producer of a product labeled with clone claims should be able to demonstrate that all milk-derived ingredients in the product are from non-cloned cows. Failure to maintain records would make it difficult for a firm to defend itself in the face of circumstantial evidence that it is using or selling milk from cloned cows. In some situations (e.g., dairy cooperatives that only process milk from non-cloned cows), States may decide that affidavits from individual farmers and processors are adequate to document that milk or milk products received by the firm were from non-cloned cows.

States should consider requiring that firms that use statements indicating that their product is “certified” as not from cloned cows be participants in a third party certification program to verify that the cows are not clones. States could seek to ensure that certification programs contain the following elements: Participating dairy herds should segregate milk from cloned cows. The program should be able to track each cow in the herd over time. Milk from non-cloned cows should be kept separate from other milk by a physical segregation, verifiable by a valid paper trail, throughout the transportation and processing steps until the finished milk or dairy product is in final packaged form in a labeled container. The physical handling and recordkeeping provisions of such a program would be necessary not because of any safety concerns about milk from cloned cows but to ensure that the labeling of the milk is not false or misleading.