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DEPARTMENT OF ANIMAL SCIENCE
ONE SHIELDS AVENUE
DAVIS, CALIFORNIA 95616.8521
TELEPHONE: (
FAX: (

Regulations Review
Office of the Gene Technology Regulator (MDP 54)
GPO Box 9848, Canberra ACT 2601
Australia

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My name is Alison Van Eenennaam, and I am an animal geneticist at the University of California in Davis, a position I have held since 2002. I hold a Bachelor of Agricultural Science from The University of Melbourne in Australia, and both a Masters in Animal Science and Ph.D. in Genetics from The University of California in Davis. I have an active research and outreach program, and my specialty is animal biotechnology and genomics, with a focus on using genetics to solve applied problems of animal agriculture.

I am responding to your request to address consultation questions relative to options for regulating new technologies:

1.Which option/s do you support, and why?

I support option 4 because scientifically it is illogical to regulate genetic changes that are similar to or indistinguishable from the products of conventional breeding differently based upon the breeding method that was used to create the change. The risk posed by the products does not differ. The trigger of “a novel combination of genetic material” is included in some of the international regulations (e.g. Cartagena Protocol) associated with the regulation of genetically engineered organisms, and this seems a reasonable place to make the distinction between what triggers regulation and what does not. Ideally it would be based on the novelty of the product, but I understand that discussion is off the table. Therefore a knockout produced by site-directed mutagenesis and non-homologous end joining, or intraspecies allele substitution which does not introduce “a novel combination of genetic material” and would therefore be excluded. We have worked on developing polled cattle that have an intraspecies allele substitution (the polled allele from Angus substituted into Holstein germplasm), and have sequenced the resulting animals (**1**). The only genetic change that can be detected (above the normal background sequencing error and spontaneous mutation noise) is the intraspecies allele substitution. It is unclear what unique risks are associated with this approach to introducing the polled allele (**2**) into Holstein genetics, that differ from those associated with crossbreeding of an Angus bull to a Holstein cow (or vice versa).

2. Are there other risks and benefits of each option that are not identified in this document?

I think the opportunity costs of forgone benefits based on the current regulations around genetically engineered animals is considerable. Despite the fact that the genetic engineering of animals preceded the development of approaches to achieve the same outcome in plants over 30 years ago, there are no genetically engineered animals for food purposes available commercially anywhere in the world. If options 1-3 are considered then intraspecies allele substitution using site-directed nucleases will be regulated, and it is unclear what unique risks are associated with this approach that are not also associated with conventional crossbreeding. As such this would introduce a level of regulation that is not commensurate with the risks posed by the gene technology.

3. Is there any scientific evidence that any of options 2-4 would result in a level of regulation not commensurate with risks posed by gene technology?

I will use the case study of the polled Holsteins to ask what unique risks might be posed by a “horn-less” Holstein that are not also posed by a “horn-less” Angus or “horn-less” Hereford carrying the polled allele?

4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme?

   I believe it is important to understand that a lot of animal breeding relies on the combination of multiple lines to make the commercial hybrid that is the saleable product of animal breeding programs. As such, if new technologies are to be used in breeding programs, multiple edited founder individuals in different parental strains will need to be produced. If each individual animal has to go through a separate regulatory evaluation irrespective of whether the phenotype is actually novel, or whether the genetic changes it carries are similar to or indistinguishable from the products of conventional breeding, then this regulatory burden will effectively act to discourage the use of these new technologies in animal breeding programs. The opportunity cost of this would be considerable especially given the potential of these new technologies to be used to produce animals with traits such as disease resistance (**3**).

   Regulatory systems provide one way for society to find a balance among the potential benefits, risks, and concerns associated with new technologies. Regulatory effort should be proportional to risk posed by the product being evaluated. The current regulatory system for the products of genetic engineering is lengthy and prohibitively expensive for all but large, multinational corporations. Currently identical products produced using different breeding methods are subject to vastly different levels of regulatory scrutiny. This is scientifically unjustified, and is disincentivizing the development of beneficial applications to the detriment of global food security and agricultural sustainability. I hope that the eventual option that is selected for regulating these new technologies is triggered by, and commensurate with, novel risks and also weighs these against potential benefits. Ideally oversight would be exercised **only when the value of the reduction in risk obtained by additional oversight is greater than the cost thereby imposed** and evaluated against the potential benefits that would result from the use of the new technology to produce specific genetic changes on a case-by-case basis.

References

(1) Carlson DF, Lancto CA, Zang B, Kim E-S, Walton M, Oldeschulte D, Seabury C, Sonstegard TS, Fahrenkrug SC: **Production of hornless dairy cattle from genome-edited cell lines**. *Nat Biotech* 2016, **34**:479-481.

(2) Carroll D, Van Eenennaam AL, Taylor JF, Seger J, Voytas DF: **Regulate genome-edited products, not genome editing itself**. *Nat Biotech* 2016, **34**:477-479.

(3) Van Eenennaam, A.L. 2017. **Genetic Modification of Food Animals**. *Current Opinion in Biotechnology* 44:27-34.

Yours Sincerely,

Alison Van Eenennaam, PhD
Cooperative Extension Specialist
Animal Genomics and Biotechnology
Department of Animal Science
University of California
One Shields Avenue
Davis, CA 95616
USA