recombinetics

18 April 2018
Food Standards Australia and New Zealand
Food derived using new breeding techniques - review
15 Lancaster Place
Majura Park ACT 2609

Re: Submission: Consultation Paper- Food Derived Using New Breeding Techniques

Dear Mr. Booth,

Recombinetics, Inc. (RCI), St. Paul, Minnesota, appreciates the chance to provide this submission in response to the Consultation Paper – Food Derived Using New Breeding Techniques. RCI believes that clarity is urgently required in the assessment and management of New Breeding Technologies (NBTs) across the diversity of current and future applications. We hope this clarity is based on risk commensurate with the known facts about these technologies and our deep knowledge as a species of genetics and genomics, which has expanded exponentially since the completion of thousands of genome projects over the past 20 years.

As a small start-up company formed in 2008, Recombinetics (RCI) has focused its initial efforts on developing gene editing technologies and intellectual property for livestock applications in biomedical models, regenerative medicine, and food animal agriculture. Due to our broad scope of application development and demonstrated ability to produce food animals with improved well-being, our company has explored numerous commercial opportunities to invest and partner with genetic providers within Australia and New Zealand. However, these opportunities continue to be constrained by uncertainty in regulation associated with gene editing and a lack of national consistency in the application of the legislation. Again, we hope this process and the information we provide on use of new breeding technologies in the animal sector help provide clarity and alignment to regulation in Australia.

Thank you for the opportunity to share our views. Please feel free to contact me if you there are any questions or a need for further information.

Sincerely,

Tad Sonstegard Ph.D.
Chief Scientific Officer of Acceligen
A Recombinetics Company

Recombinetics Inc. Submission

Background and Scope

Recombinetics Inc. (RCI) was founded in 2008. We are the premier gene-editing company in livestock, with applications in sustainable and accelerated animal breeding and production (e.g. animal welfare, meat and milk quality, disease resistance, fecundity) as well as two non-food divisions with more than 50 biomedical swine models targeting genetic disease, cancer research and regenerative medicine.

Recombinetics has several gene edited products that demonstrate the power and value of the technology. For one of these, RCI demonstrated that a significant animal welfare issue for the cattle industry could be eliminated (Carlson et al., 2016). That is, elite cattle could be genetically dehorned, alleviating the need for the physical removal of horns. This has direct on farm cost and social benefits to farmers, social benefits to consumers; as well as supporting the welfare of the animals.

RCI has also develop precise swine models of patient congenital and progressive diseases, including neurodegenerative diseases, heart disease, diabetes, and cancer. RCI's proprietary pig models are used by world-renowned clinics and hospitals, and medical device and pharmaceutical companies to enable more rapid commercialisation of safe and effective biomedical products with lower costs.

It is our belief that gene editing offers the first biotechnology methods that truly provide economically feasible opportunities to revolutionise genetic improvement of food animals with naturally occurring and novel traits as well as eliminate genetic based animal and human diseases. We also believe some of the traits we have researched and developed are ready for commercial deployment by meeting the relatively high standards of industry's animal breeders, whom require that precision bred animals be deployed without disrupting both the value chain of production and ongoing genetic progress driven by sophisticated genomic selection systems.

Based on our commercial goals for genetic improvement of food animals, RCI welcomes this opportunity to respond and comment on the Consultation paper: Food derived using new breeding techniques, and the consideration of the definitions in the Australia New Zealand Food Standards Code for 'food produced using gene technology' and 'gene technology'.

RCI Response to Consultation Questions

3.1.1 Do you agree, as a general principle, that food derived from organisms containing new pieces of DNA should be captured for pre-market safety assessment and approval? Should there be any exceptions to this general principle?

As worded, the general principle is already biased towards the pre-cautionary principle and has confusing language. The adoption of this general principle advocates a regulatory trigger based on a process or method that is not clearly defined nor based on risk. Therefore, RCI **does not agree** that any food derived from organisms containing new pieces of DNA (undefined as to what is considered new DNA) should be

captured for pre-market safety assessment and approval. RCI believes the trigger for pre-market safety assessment and approval should be matrix based framed by our knowledge of genomes, system biology, and genetics. Its use should only be required if the final matrix characteristics of the food warrant such an assessment or if the resultant animal is a biomedical model where animal well-being needs to be considered. Founder animals produced using NBTs that cause unintended genetic disease or don't meet phenotype expectations will be naturally triaged in a pre-market scenario because breeding companies and producers usually do not purchase or breed animals that have lower market value potential or are worse in performance than the previous generation. Furthermore, lethal mutations are never born or do not fully develop. In this sense, the industry and the animals regulate themselves or they do not survive.

The introduction of 'new pieces of DNA' should be more clearly defined. As a company that does precision breeding of food animals using different gene editing methods to introgress naturally occurring alleles, we feel our processes would fall outside the definition of the general principle. This is because non-homologous end joining (NHEJ), NHEJ combined with homology directed repair (HDR), and base editing do not require any new pieces of DNA to be incorporated into the target genome. Thus, the edited genome of the cell or embryo selected to make an animal by advanced reproductive methods will eventually produce (or its progeny will produce) food that is indistinguishable from those that could be made by conventional breeding. Logically, none of these outcomes have any risk; because we have been eating the products of the natural alleles, sometimes for centuries.

3.1.2 Should food from null segregant organisms be excluded from pre-assessment and approval?
If yes, should that exclusion be conditional on specific criteria and what should those criteria be?
If no, what are your specific safety concerns for food derived from null segregants?

The generation and use of null-segregants **should not require pre-assessment and approval**. RCI believes there is no scientific rationale that could even hypothesize how a null segregant could pose a risk as a living organism or as a food product. Organisms lose and gain genetic differences all the time through natural mutation; and a null segregant is no different from these organisms except that it was derived from a founder that was transgenic. We don't believe null segregants from gene edited animals will ever be produced, because the parent is transmitting mutations (stable) not transgenes (except in cases of SDN-3). RCI also believes, IVF embryos that have undergone gene editing treatment, but fail to introduce (or retain) the edit due to site-directed nuclease inactivity (or over activity) should be considered as non-gene edited animals. Some embryos will still have value, even when not edited, due to the need to make founder animals from elite genetic matings. Part of industry acceptance of this technology will rely on regulatory relief of treated but not edited animals.

RCI agrees with the recent OGTR proposal that organisms derived from GMOs that have not inherited traits that occurred because of gene technology (null-segregants) not be considered a 'GMO' and therefore not be regulated under the *Gene Technology Act 2000*.

3.1.3 Are foods from genome edited organisms likely to be the same in terms of risk to foods derived using chemical or radiation mutagenesis? If no, how are they different?
If yes, would this apply to all derived food products or are there likely to be some foods that carry a greater risk and therefore warrant pre-market safety assessment and approval?

New breeding techniques based on cellular DNA repair (SDN-1 and SDN-2) are the only methods of mutagenesis appropriate for developing new traits or introgression of proven traits into food animals. The

precision of these methods is absolutely required to be commercially feasible. Use of chemicals and radiation to develop new traits is not practical or economical due to the low efficiencies and cost of advanced reproductive methods. Use of these random mutagenic reagents on germ cells in adults is also a potential problem when considering animal well-being. So, for food animals, gene editing is the only innovative breeding method available for developers to overcome challenges of traditional breeding and selection.

RCI advocates the same regulatory treatment of products developed with new breeding technologies to those that can similarly be obtained with various 'conventional' tools – such as use genomic selection of the allelic variation within an animal and use of mutagenic reagents in plants. It should be pointed out, the application of DNA repair mechanisms induced by site-directed nucleases already has a body of literature with more than 20,000 peer-reviewed articles, and this process is the same as any induced by a double strand break in the DNA caused by unregulated mutagenic agents.

3.2 Are you aware of other techniques not currently addressed by this paper which have the potential to be used in the future for the development of food products?
Should food derived from other techniques, such as DNA methylation, be subject to pre-market safety assessment and approval?

RCI stands by our scientifically supported position that regulation must be proportionate with risk. Pre-market safety assessment and approval should only be triggered when the final characteristics of the food (all cases) or animal phenotype (in some cases) are changed (i.e. if it is hypoallergenic – prove it; if it is a novel disease resistant sequence variant – prove it). Such cases could warrant pre-market assessment of risk. This risk should be based on genome conservation and known systems biology information and should not be based on the process used to produce the product.

The application/addition of regulation should adhere with the principles outlined in The Australian Government Guide to Regulation.

3.3 Do you think a process-based definition is appropriate as a trigger for pre-market approval in the case of NBTs? If no, what other approaches could be used?
If yes, how could a process-based approach be applied to NBTs?
Are there any aspects of the current definitions that should be retained or remain applicable?

RCI supports regulation based on risk based backed by scientific rationale. Ultimately, gene editing outcomes can produce an indistinguishable food product even if animal phenotype was altered (i.e. genetic dehorning or adaptation to tropical conditions). Eventually, if innovative use is allowed and multiplex editing solutions are developed; then many of the gene edited targets could be quantitative traits in nature (changing production amounts or efficiencies incrementally). Pre-market approval schemes would be difficult to be logically developed, especially if so many of the changes were to non-genic regions or methylation signals. Thus, RCI would contend that definitions be developed that examine the risk of the 'end-product' rather than the process to make it. The highly competitive nature of the food animal genetics commercial market provides a built-in system of pre-market review and post-market surveillance. These commercial efforts are already part of the system for animal breeding, especially in cattle. At the current time, most breed association have told us that they want to know the economic

value of traits (pre-market) and track gene edited animals – not out of concern for food safety – but to be able to calculate, track, and market the value of animals improved by gene editing. If definitions are put into place, then they should clarify what modifications would require pre-market safety assessment and approval (e.g. modifications that impact food allergenicity or toxicity). Other allelic changes that have a history of safe use and value should not require such assessment.

3.4 Are there other issues not mentioned in this paper, that FSANZ should also consider, either as part of this Review or any subsequent Proposal to amend the Code?

Regulatory alignment

Because of the somewhat complex system and its current renovation in Australia – as outlined in the three bullets below:

1. Technical Review of the Gene Technology Regulations (lead by the OGTR).
2. Review of the National Gene Technology Regulatory Scheme (lead by the Department of Health).
3. Review of Food Derived Using New Breeding Techniques (lead by FSANZ).

RCI supports efforts for government agencies to align regulations as much as possible to promote innovation with a simple and clear systematic path to market that is not burdened by regulatory timing and complex processes. For food animals, time is of the essence. If an edited animal cannot make it to the commercial market with a speed equivalent to those non-edited animals under genomic selection, then NBTs will not be used except in specialty cases of nominal economic value.

Citations

Carlson DF, Lancto CA, Zang B, Kim ES, Walton M, Oldeschulte D, Seabury C, Sonstegard TS, Fahrenkrug SC. Production of hornless dairy cattle from genome-edited cell lines. Nat Biotechnol. 2016 May 6;34(5):479-81. doi: 10.1038/nbt.3560