recombinetics

21 February 2018

To: The Regulations Review
The Office of the Gene Technology Regulator (MDP 54)
GPO Box 9848
Canberra ACT 2601
OGTR@health.gov.au

Re: Recombinetics' submission in response to the Regulation Impact Statement for Consultation: Updating Gene Technology Regulation in Australia and the draft amendments to the Gene Technology Regulations (GT Regulations)

Dear Sir or Madam:

Recombinetics, Inc. (RCI), St. Paul, Minnesota, U.S.A. is pleased to submit comments to the Office of the Gene Technology Regulator (OGTR) from the Australian Government's Department of Health in response to proposed amendments of the Gene Technology Regulations.

Framing Our Response

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 using SDN1 and SDN2 methods, we were fully supportive of Option 4 during the OGTR consultation of 2016 for the Technical Review of the Gene Technology Regulations 2001.

This current submission is specifically in response to the Exposure Draft Regulations on the understanding that there are probably limited possibilities to amend the GT Regulations using the current policy framework. RCI is encouraged that the proposed amendments are an incremental step towards developing a better science-based risk assessment of the new breeding technologies that use site-specific nucleases (SDN). However, we still maintain that the best legal framework for determining if a gene edited organism is a GMO or not should be based on the end genome product not the process by which the allelic variation was introgressed into a genome. We expand on this major point below.

Recombinetics Response to Consultation Questions

1. *What is your preferred Option? Please explain why.*

RCI supports Option 3 that proposes to amend the Gene Technology Regulations (GT Regulations) with some but not all draft amendment proposals, as detailed in Section 3 of the Consultation Regulation Impact Statement.

We believe most of the amendments proposed in the Exposure Draft Regulations are very reasonable, but several proposed changes need more deliberation to ensure Australia will stay aligned with rapidly changing applications of the new breeding technologies. For example, regulation of animals or plants changed with base editors, which allow direct and irreversible sequence conversion without breaking DNA strands, would already seem unclear in the new amendments.

2. *Do the draft amendments clearly implement the measures described in Section 3 of the Consultation RIS? If not, which areas of the draft amendments do you think require additional clarification, and what clarification is needed?*

RCI believes that the proposed amendments largely implement the measures described in Section 3 of the Regulation Impact Statement for Consultation. However, RCI suggests the following elements require further consideration.

1. Schedule 1 – New Schedule 1B (Item 31).
2. Schedule 1 – New Item (Item 32) Organisms modified using SDN-1 are not GMOs.
3. Schedule 1 – two new Items (Item 33) Organisms derived from GMOs.
4. Schedule 2 – Repeal Schedule 1 (Item 1).

Schedule 1 – New Schedule 1B (Item 31)

RCI does not support the regulation of SDN-2 alterations as GMOs as proposed in the new Schedule 1B. As discussed in our previous submission, RCI supports that certain breeding applications should be excluded from regulation based on outcomes. RCI has already demonstrated an ability to make polled animals using SDN-2 methods, and the replaced allele (non-genic) is indistinguishable from one that can be introduced by conventional breeding. This polled allelic variant is in millions of cattle and has been eaten safely for at least a thousand years. How can the identical allele pose any risk or be tracked within the supply chain as a GMO product? Thus, we believe strongly that there are very clear cases where the GT Regulations should allow techniques that use SDN-2 to not be regulated as GMOs. Furthermore, regulation of SDN-2 altered genomes, like genetically dehorning cattle with the *celtic* allele, imposes unnecessary regulation on techniques that should be considered equivalent in function and risk to SDN-1 (i.e. no risk scenarios). Thus, RCI would suggest that some genome editing techniques should be defined as mutagenesis techniques under Schedule 1A. We also still contend that HDR templates, regardless of size, should be considered as mutagenic elements of the DNA repair process (i.e. non-residual chemicals), which just happen to allow this process to be very precise and specific.

Schedule 1 – New Item (Item 32) Organisms modified using SDN-1 are not GMOs
RCI supports the classification of organisms with SDN-1 derived alterations as non-GMOs. RCI is confused that the term SDN-1 may still be considered a gene technology (Schedule 1A). We suggest there is a need to better define what is not considered gene technology by revising Schedule 1A to more broadly define products that result from a dsDNA break and repair using the non-homologous end-joining process or by irreversible base conversion (base editors) as non-gene technology products.

Schedule 1 – two new Items (Item 33) Organisms derived from GMOs
RCI supports the need for clarification on the regulatory status of organisms descended from a GMO. This provides some relief in the massive costs associated with wasteful disposal of recipients, siblings, and co-mingled animals that encountered gene edited animals produced using SDN-2 or SDN-3 methods. However, we believe there is still some uncertainty in the proposed amendments. Again, we use our example of genetically dehorned cattle bred using SDN-2 methods. Under the current amendments, these animals are considered GMO even though no foreign DNA was introduced during the allelic introgression. Furthermore, the new allele is an exact copy of a naturally occurring mutation enriched in cattle through artificial selection. Would the descendants of these founder polled animals be considered GMO? How would the generations of offspring be tracked as a GMO for a naturally occurring allele?

Schedule 2 – Repeal Schedule 1 (Item 1)
RCI prefers that the Regulator maintain Schedule 1 Item 1 to maintain clarity about those mutagenic techniques that have a history of safe use, and recommends that the term chemical mutagenesis be clearly defined under Schedule 1A in terms that includes new breeding technologies like genome editing.

3. *If your preferred option is Option 3, please indicate which amendments (or parts thereof) you support being progressed and why.*

Except for those with comments above in Section 2, RCI supports the OGTR's proposed amendments to the GT Regulations.

4. *What are the costs and benefits to you or your organisation from the proposed amendments? Please describe these compared to current arrangements, for each area of amendment.*

We believe regulatory relief of animals created by SDN-1 methods will have significant benefits in cost and time reductions needed for this technology to complement and integrate in with current practices of genetic improvement for livestock and aquaculture. Once again, the

proposed regulation of SDN-2 will restrict or hinder some commercial opportunities, even though our ability to safely introgress naturally occurring alleles has enormous potential for enhancing animal well-being and producing products beneficial to both human health and to agriculture.

5. *Are the proposals to change the classification of certain NLRDs and exempt dealings (identified in Appendix B of the Consultation RIS) commensurate with any risks to the health and safety of people and the environment posed by the dealings?*

RCI maintains the view that organisms modified by SDN-2, especially if the mutagenic conversion only swaps one naturally occurring allele for another, should not be classified as GMOs. Most in the commercial livestock genetics business, already accept that there in transmission and consumption of naturally occurring alleles in animals, and we already have a proven method to manage risk, if any, by using genetic selection of our breeding stock.

6. *Are there any features in the options presented that you have concerns with? Or, are there any particular features that you believe should be included? Please explain why and give substantiating evidence where possible.*

RCI would just underscore that there is an urgent need for regulation to keep pace with innovation. Since the original GT Regulations were drafted, hundreds of plant and animal genomes have been sequenced and hundreds of thousands of peer-reviewed articles have been published that document our deeper understanding of genetics, genomics, and systems biology. Our hope is that these major advances in our knowledge are considered prior to developing future, more substantial changes in policy framework for risk assessment. Otherwise, the full potential of these rapidly changing new breeding technologies will never be realized as commercial opportunities for genetic improvement of food species or as tools of change to meet challenges of global food security.

Thank you for the opportunity to provide comments on these proposed amendments.

Sincerely,

Tad Sonstegard
Chief Scientific Officer of Acceligen - Recombinetics, Inc.