10 December 2016

INTRODUCTORY INFORMATION PROVIDED BY THE OGTR

The following are quoted from the Gene technology Regulator's discussion paper. They are provided below for readers' information only and are not part of our submission.

OPTIONS

Option 1: No amendments to the GT Regulations

Option 2: Regulate certain new technologies

Option 3: Regulate some new technologies based upon the process used

Option 4: Exclude certain new technologies from regulation based on the outcomes they produce

EXPLANATION

Option 1 is being put forward for consultation to ask whether the current situation is better than any of the other options being proposed.

Option 2 proposes to amend the GT Regulations so that dealings with all organisms developed using oligo-directed mutagenesis and all site-directed nuclease techniques are regulated under the GT Act.

Option 3 proposes that the use or absence of nucleic acid template to guide DNA repair determines whether techniques are regulated under the GT Act. That is, techniques where nucleic acid template is applied to guide DNA repair (i.e. oligo-directed mutagenesis and the site-directed nuclease techniques known as SDN-2, SDN-3) would result in GMOs, whereas some specific techniques which do not involve the application of nucleic acid template (i.e. the site-directed nuclease technique known as SDN-1) would not result in GMOs.

Option 4 proposes to exclude organisms from regulation as GMOs if the genetic changes they carry are similar to or indistinguishable from the products of conventional breeding (e.g. chemical and radiation mutagenesis methods and natural mutations). This would have the effect that dealings with organisms produced by oligo-directed mutagenesis and SDN-1 and SDN-2 would be excluded from regulation.

10 December 2016

SUBMISSION FROM RPAH IBC

Royal Prince Alfred Hospital IBC (RPAH IBC) considered the Regulator's consultation questions and options for regulating new technologies at its meeting on 25 November 2016 and responds as follows.

CONSULTATION QUESTIONS

1. Which option/s do you support, and why?
Of the four options, the IBC supports option 3 (i.e. 'Regulate some new technologies based upon the process used') as it is considered to be most likely to:

- Remove ambiguities from the Gene Technology Regulations
- Facilitate regulation commensurate with risks posed
- Fit within the current policy setting of the Gene Technology Act, which is not the subject of the review (i.e. it is compatible with the process-triggered definition of 'GMO' in the Act)

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

The IBC considers that the key risks and benefits have been identified.

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?

Option 2 would result in a level of regulation not commensurate with risks posed because SDN-1 would be regulated under it. Although modifications using SDN-1 may be more or less site-specific, a repair template is not used and resulting mutations are the product of natural nucleic acid repair mechanisms in host cells. Organisms resulting from SDN-1 are likely to be similar to naturally mutated organisms or organisms resulting from conventional mutation breeding programs or from chemical or radiation mutagenesis (which do not fall under the current Regulations) and are likely to be regulated as such in many jurisdictions outside Australia.[1]

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

Compared to option 3, options 2 and 4 are likely to increase the regulatory burden on IBCs, companies, researchers and developers because:

- Option 2 would require proposals for modifying organisms using any ODM or SDN technique to be assessed by an IBC irrespective of the level of risk and trade between jurisdictions with different approaches to regulation is likely to be affected.
- Option 4 may lead to difficulties in determining which of SDN-2 or SDN-3 might apply and the degree of similarity (or otherwise) between a modified organism and its more conventional parent (as some alterations in properties may not be detectable). An

increased reliance on description as the basis for decisions may result. It is an outcome- (or product)-based trigger and may not work well within the current policy setting of the Act (which relies on a process-triggered definition of 'GMO').

5. How do you use item 1 of Schedule 1, and would it impact you if this item was changed?

Item 1 of Schedule 1 states that a mutant organism is not a GMO if *'the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)'*. We use it to explain why some organisms are not considered GMOs (such as mutant organisms resulting from spontaneous mutations).

In its current form, item 1 is not helpful in assessing new technologies that modify genetic material (or function) without introducing exogenous or heterologous nucleic acids. We recommend that it be changed to make it more useful with respect to new technologies and option 3.

Consideration could be given to whether or not an additional caveat might be useful for preventing a changed item 1 applying to organisms (such as some pathogenic microorganisms) generated by a new technology if the modified organisms are considered likely to have increased capacity to cause harm as a consequence of the new technology. A suggestion for consideration is:

'…provided the modification is unlikely to increase the capacity of the modified organism to cause harm in otherwise healthy human beings, animals, plants or fungi').

This could assist as understanding of the risks of new technologies develops (for example with respect to outcomes and off-target effects).

6. Might contained laboratory research on GM gene drive organisms pose different risks to other contained research with GMOs, and how could these risks be managed? Supporting information and science-based arguments should be provided where possible.

The potential for GM gene drives to promote the dissemination of GM genetic elements through populations at a percentage and rate greater than expected from normal Mendelian inheritance patterns poses new risks for contained research with GMOs, particularly when gene editing tools such as CRISPR/Cas9 are involved. The risks are being explored by us and many in the community.[2],[3] The ability to accurately predict risks and design effective containment strategies are not yet fully understood and a cautious approach is needed.

Our IBC deals with proposals for basic and clinical research that are medically related. Within the context of basic research the main foreseeable risks would relate to persons, animals and microorganisms; for example, accidental introduction of a gene drive into a person or an unintended release of a gene drive or a gene drive-modified animal or microorganism (such as a bacterium or virus). The nature of vectors (if used) may also be an

added source of risk. Some organisations (such as UC San Francisco) have incorporated an assessment and containment plan for gene drive research into their biosafety risk assessments[4] and we would do likewise where warranted.

We support recommendations for:

- the employment of at least two additional stringent confinement strategies in laboratory gene drive research (over and above normal containment measures) which depending on the nature of the work could involve the use of:
    - physical, molecular, ecological and reproductive barriers
    - new work practices
    - additional PPE
    - incorporation of biosecurity arrangements and
    - specific prospective testing protocols
- risk assessment to be on a case-by-case basis, and
- limits, where warranted, on how research materials may be distributed.[5]

7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? Please provide details of the techniques and science-based arguments for whether these techniques pose risks to human health or the environment.

The main techniques used are contained research involving:

- In vitro transfection of cells with siRNAs to reduce the expression of genes (such as by inducing RNA degradation)
- Stable expression of short hairpin RNAs (shRNAs) using replication-defective conventional viral vectors (such as conventional lentiviral or adeno-associated viral vectors). The shRNAs may be used for similar purposes as the siRNAs above.

As described above these techniques have clear regulatory status. The first would be exempt and the second would be a NLRD or DNIR. These classifications would depend on whether or not the vector could transduce human cells and would be injected into animals, and whether or not the shRNA could cause a tumour or immunomodulation in humans.

However, while an animal or human-being modified by the introduction of a naked recombinant siRNA or oligonucleotide is not considered to be a GMO under Schedule 1 item 2, the regulatory status of the act of introducing the siRNA or oligonucleotide into an animal or human being is less clear. This has been variously viewed as exempt (under Schedule 2, Part 1, items 3 or 3A) or as a non-GMO dealing (under Schedule 1 item 2) even though both these classifications do not describe the event itself. It is clear that, provided the siRNA or oligonucleotide cannot give rise to an infectious agent and the target is appropriate, the risks of these techniques would be negligible. Human trials using recombinant siRNA or oligonucleotides are subject to review by HRECs and fall under the TGA's remit. We would like it to be made clearer in the Regulations that the act of introducing (e.g. injecting) an siRNA or oligonucleic acid into an animal or human being is not a GMO dealing if it meets the requirements of the classification that applies to it (see also 8 below).

8. Do you have proposals for amendments to any other technical or scientific aspects of the GT Regulations? All proposals should be supported by a rationale and a science-based argument.

We would like the term 'naked nucleic acid' (as described in Schedule 1 item 3 and as used in Schedule 1 item 2) to be better defined in the Regulations.

Consideration could be given to whether or not some types of nucleic acid coatings may be low risk because of the way they facilitate entry to cells. For example, some might not be expected to favour integration into the host genome or entry into cells by receptor-mediated transduction (or have a defined sero- or pseudo-type). The status of various lipid, protein and nano-particle coats could be addressed.

This would help us assess the regulatory status of clinical trials using siRNA and oligonucleotides in humans (and animals) (referred to in 7 above).

REFERENCES

1. Sprink T, Eriksson D, Schiemann J, Hartung F. Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. *Plant Cell Rep.* 2016;35:1493–1506.
2. AAS. Discussion Paper - Gene Drives In Austraila. November 2016.
3. NAS. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. 2016.
4. UCSF. Biosafety Program - Gene Drives. 31 Oct 2016.
5. Akbari OS, Bellen HJ, Bier E, et al. BIOSAFETY. Safeguarding gene drive experiments in the laboratory. *Science.* 2015;349(6251):927-929.