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The Regulations Review
Office of the Gene Technology Regulator (MDP 54)
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Dear Sir/Madam,

On behalf of Clinical Network Services (CNS) Pty Ltd and the CNS Institutional Biosafety Committee (CNS IBC), we are pleased to be given this opportunity to provide input into the options for regulating new technologies within the framework of the current Gene Technology Act (2000) and with potential amendments to the Gene Technology Regulations (2001). CNS details almost exclusively with genetically modified organisms for human therapeutic use which is reflected in the responses in this document. Below are our responses to the questions provided in the OGTR's "Options for regulating new technologies", discussion paper (October 2016).

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

The four options provided are:

- Option 1: no amendment to the GT Regulations
- Option 2: regulate certain new technologies
- Option 3: regulate some new technologies based on the process used
- Option 4: exclude certain new technologies from regulation on the basis of the outcomes they produce.

For the purposes of therapeutic medicinal products for human and animal use, we feel Option 4 would be the most appropriate.

For example, regarding Option 4 as stated in the discussion paper, this would not change the GT Act of the process-triggered definition of a 'GMO' but could result in a change to the GT regulations of "techniques that are not gene technology" in Schedule 1A or the list of "organisms that are not GMOs".

We support Option 4 for technologies that are currently "borderline" GMOs, such as an attenuated vaccine, that have not taken an existing organism and introduced genetic modifications (thereby, by logical definition we feel should not be considered a GMO).

The risks of such a product could be adequately managed using safe guards inherent in clinical trials under existing legislation. Subsequently, the risks to environment and public health could be managed by separate environmental risk assessments during development to support a registration application with the Therapeutic Goods Administration.

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

Option 1; we agree that the GT regulations do need to be updated in line with advances in technology over the past 15 years since the Regulations came into effect.

Option 2; we agree that capturing all oligo-directed mutagenesis / site-directed nuclease techniques under the GT regulation would provide industry with clarity but may not be commensurate with the risks posed by these technologies and so we do not favour this option. As with the example above, the vaccine that is produced using this technology is indistinguishable from the wild-type virus (aside from the high level of attenuation), thereby differentiation between the vaccine and the wild-type organism would not be possible without sequencing the virus.

Option 3; we feel that, although preferable to Options 2 and 1, Option 3 may create uncertainty as to which products/processes would require regulation under the GT Regulations which would have commercial implications for development of new technologies in Australia compared to competing countries for clinical trial and drug development research. The existing regulatory framework for GMOs, adds at least 6 months to a GMO clinical study and this places Australia at a disadvantage globally.

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?**

Considering GMO products that are live attenuated vaccines, where the genetic modifications have resulted in a less virulent form of the wild-type virus, we consider the current level of regulation not to be commensurate with the level of risk (especially given the safe guards that exist under the current clinical trial scheme implemented under NHMRC and TGA legislation). Many of the environmental concerns that are raised by the OGTR are hypothetical and difficult to challenge scientifically. For example, potential for reassortment of a vaccine with a wild-type form resulting in a more virulent/ different virus or the risks are readily managed by universal precautions, hand washing and waste disposal policies that are regulated practice at these clinical trial sites.

We feel that the approach to regulating GMO technologies should be based on both risk and benefit, rather that purely on risk. This is especially relevant for medicinal products to treat diseases that have high unmet clinical treatment options

(i.e. gene therapies) for patients with rare genetic diseases. The current legislation imposes a 6 month delay on patients accessing these therapies on the basis of risk to the environment and the public without substantial evidence of these risks and where hypothetic risks are possible, the risks are readily mitigated by the policies and practices at these clinical sites discussed above.

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

Generally, we feel the regulatory burden of obtaining and maintaining a DIR or DNIR licenses for human medical GMO products under the current GT regulations is, in many cases, not commensurate with the risks they pose and more onerous than the requirements of other highly regulated countries (i.e. USA).

For example, Australia attracts international companies to perform clinical trials here because of the pragmatic and rapid processes in Australia to approve clinical trials, which are less onerous than the US and Europe. However, for GMO products, the requirement to obtain an OGTR license adds significant cost and extension of timelines (at least 6 months) to be able to import the product into the country. For commercial release applications, the delay is at least 12 months for a product that have been marketed and released outside Australia. In addition, if the OGTR decide to audit clinical trial sites, who work under international Good Clinical Practice guidelines, significant additional resource and costs for the Sponsor companies is required. This results in Australia being a less attractive country to perform trials in which has detrimental consequences to both potential patients and the economy.

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, *Organisms that are not genetically modified organisms*, "A mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)."

We interpret this quite literally as an organism which has not had foreign DNA from another species introduced, is not a GMO. Clarification around this definition, in particular what constitutes a "foreign nucleic acid" would provide additional clarity.

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**.

Contained laboratory research does reduce the risks of environmental exposure compared to human and animal therapeutic GMOs and non-contained

commercial plant GMOs. As is currently the case, the type of GMO and the ability to contain it, should be factored into burden of regulation taking into account both the risks and benefits of the GMO in question and how other processes (i.e. clinical trials) manage these risks. For example, all infectious waste is either incinerated or chemically inactivated according to State EPA legislation. Mandating at a federal level, existing state legal requirements does not specifically manage the risks of a GMO. It only adds red tape to the process of researching these potential therapies.

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.**

As a Contract Research Organisation, we do not directly use RNA interference techniques. Although a number of clients are currently considering this technology as a therapeutic modality (e.g. to silence viral gene expression and interrupt replication of chronic viral pathogens such as Hepatitis C virus).

Therapeutics involving the introduction of siRNA or miRNA should not be considered a potential risk to human health or the environment. RNAi methods involve the use of synthetically produced small naked RNA molecules (siRNA/shRNA/miRNA 18-60 nucleotides in length). They are unable to self-replicate in host cells, therefore propagation and integration into the host genome is not possible. As this mechanism occurs naturally in plants, animals, and fungi, there is far reaching evidence to suggest that effectiveness and safety are measurable and documented. Targets are sequence specific, therefore the potential for off-target gene silencing is drastically reduced and outside the mechanism's functionality. Use of such molecules provides transient gene regulation before target cells undergo natural cell death – therefore these unstable molecules are degraded quickly and not released into the environment.

There are several commercial delivery systems available that *would* involve the introduction of foreign DNA into host cells for effective RNA mediated interference. With this in mind, particular RNAi techniques would use gene technology to produce GMOs, including but not limited to plasmid-expressing miRNA or shRNAs, viral vectors (Adenoviruses, Lentiviruses, Baculoviruses, Mouse stem cell virus, etc), PCR-generated siRNA/shRNA/miRNA expression cassettes, and more recently CRISPR/Cas9 gene editing systems. As viral vectors are able to integrate small RNAs into host chromosomal DNA for long-term consistent expression, this leads us to suggest that Option 3 (regulate some new technologies based on the process used) should be applied to RNAi technology depending on the risk of integration.

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 propose that in *Schedule 1A—Techniques that are not gene technology*, consideration is given to including synthetic techniques where RNA / DNA are synthetised. Consequently, the resulting products are well characterised with precise reproducibility.

Regarding the licence requirements themselves, we have found them to be repetitive and in some cases contradictory, making it confusing and difficult for the concerned parties to be confident they are in compliance with their licenses. In our opinion, it would be preferable if the OGTR provided a concise background to their decisions followed by a clear list of non-ambiguous conditions.