



18 November 2016

Regulations Review  
Office of the Gene Technology Regulator (MDP 54)  
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ACT 2601  
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Dear Regulator,

**Re: Response to discussion paper: Options for regulating new technologies**

We understand that with the introduction of new gene-editing technologies, which now allow modification of nearly any organism, that it is prudent to examine if current GT Regulations capture all potential GMOs (except humans) and the vectors and tools used to modify the parental organism. The experience of our IBC, which regularly reviews applications dealing with techniques and tools such as CRISPR/Cas9, TALENs and shRNA across a spectrum of organisms, is that the current GT regulations capture aspects of the organism, the vector, the tool and the genes being modified.

One strategy of modifying the genetics of an organism that is not presently captured by the GT regulations is deliberate and coordinated selective pressure to enrich for resistant organisms without the introduction of nucleic acid. This would include but is not limited to growing wild-type bacteria or propagating viruses that have NOT been manipulated with exogenous nucleic acid, in progressively higher concentrations of chemical agents to deliberately select for specific characteristics e.g. antibiotic resistance. This is not a new technique and it has been used for many years to select resistant mutants whose genome can then be interrogated to define the mechanism of resistance. By their nature these experiments result in mutants that can pose a risk to the community but they are considered to have occurred “naturally”.

A similar strategy is routinely used to select for mutants that have been subjected to modifications through the introduction of nucleic acid and gene-editing tools. These latter cases are presently incorporated in the GT regulations. We appreciate that mutations generated by technologies eg CRISPR/Cas9 may be identical or indistinguishable from naturally occurring mutations (or mutations occurring through ENU-mutagenesis). Naturally occurring mutants are not regulated but ‘gene technology’ driven GMOs do fall under GT regulation. We do not see this as an issue, and believe the higher regulation imposed on eg CRISPR/Cas9-generated GMOs is currently warranted especially as gene technology derived GMOs may

contain “off target” and unanticipated mutations that confer advantages over and above naturally occurring mutants. With specific reference to the consultation question we provide the following view.

1. Which option do you support and why? Option 1 as it pertains to “NEW” technologies but consideration should be given to regulating some ‘old’ techniques that select genetic mutants (see point 5 below). Applications received by our IBC must stipulate: 1. the organism being modified; 2. the vector that is being used e.g. plasmid, microinjection of DNA, lentivirus etc; and 3. the DNA/genes being introduced e.g. Cas9, sgRNA, shRNA (and what genes they target) etc. The tools that are being used to perform the gene-editing are explicit in these descriptions as are the risks involved. For example if a researcher is modifying a primary human cell line with a 3<sup>rd</sup> generation lentiviral vector encoding CRISPR/Cas9 with a guide targeting KRAS it would be clear to all IBCs working within the framework of the current regulations that the researcher is making two GMOs, that they are using primary human cells, viral vectors and the genes involved are Cas9 and KRAS modifications. This allows us to examine the risk posed by the GMOs (including cases where the vector itself is a GMO). The same would apply to TALEN and shRNA gene-editing tools. Therefore we see no need to amend GT Regulations as they already appear to capture ‘new’ technologies.
2. Are there other risks and benefits of each option that are not identified in this document? We see no benefit, and perhaps a risk, with options 2, 3 and 4 as they change regulations, unnecessarily complicate risk assessment and they distract review committees from focusing on the GMO by overstating the importance of the gene-editing tool. For example, emphasis on the gene-editing tool may distract the ability of IBCs to focus on the most important element in applications and that is the GMO and the risk it poses. The current regulations succinctly and accurately capture the risks posed by GMOs regardless of the gene-editing tool.
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 the gene technology. We are not aware of any scientific evidence to support this statement.
4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme? Options 2-4 may incrementally increase the burden of work for an IBC and researchers but the greater concern is that regulatory changes may dilute the focus from the risks posed by the GMOs and focus unnecessary attention on the gene-editing tool.

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 allows researchers to utilise organisms with mutations that have arisen naturally e.g. mice that spontaneously lose or mutate genes and bacteria and viruses that do the like. Such mutants that arise naturally through breeding/ propagation programs and even those that arise through intentional irradiation/ chemical mutagenesis are useful tools to study the genetics of phenotypes. Presently, at our Institute we do not deliberately use selective pressures to intentionally generate mutants that are resistant to antimicrobials or confer an advantage over wildtype organisms. If only this latter case were regulated it would not affect the majority of our work.
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? We believe the risk posed by laboratory research on GM gene drive organisms is similar to other contained research with GMOs that confer a selective advantage and this is presently captured by GT Regulations. As long as the phenotypes of the GMOs that are being selected are clearly stated in applications, then the risks posed by the GMO can be identified and mitigated.
7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? We presently use RNA interference mediated through vector free delivery of siRNA and vector mediated delivery of shRNA. This appears to be adequately captured in the GT regulations.
8. Do you have a proposal for amendments? See point 5 above. We are not aware of any incidents arising from the inability of item 1 of schedule 1 to encompass mutant organisms.

We hope you find our comments and suggestions useful.

Regards,

Marc Pellegrini  
Chair Institute Biosafety Committee  
The Walter and Eliza Hall Institute