

Email Submission: Robert Oppenheimer

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

Option 4.

In the long term, I think it should become the goal of the OGTR to focus on biological properties. By analogy, we do not assess the safety of chemicals by the process used to synthesise them, but instead by whether a chemical has properties that render it hazardous to human health and whether there are appropriate measures to decrease the risk of accidents. Future biotechnologies will only become more complex and diverse as genetic technologies are invented or repurposed from Nature. As such, it is wasteful and ineffective to focus on process when time and energy should be devoted to considering the biological properties considered safe.

In the short term, gene-editing is a quicker, safer version of natural or chemical mutations and should be regulated accordingly, ie, it should be generally permissible in non-human organisms. Where sufficient information is known about genotype-phenotype relationships, it will be more cost-effective than traditional breeding methods to achieve the same result (Carlson et al. 2016). Tracking the use, users, purpose and consequences of gene-editing would be desirable where it is feasible and legal.

Option 4 seems to me to resonate most with this reasoning, as it focuses on the outcomes of genetic modification - the properties of the modified organisms.

Carlson, D. F., Lancto, C. A., Zang, B., Kim, E. S., Walton, M., Oldeschulte, D., ... & Fahrenkrug, S. C. (2016). Production of hornless dairy cattle from genome-edited cell lines. *Nature biotechnology*, 34(5), 479-481.

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

I imagine that researchers may find it very frustrating if an arbitrary regulation is imposed - i.e., if a routine single nucleotide edit that is known to have occurred by naturally by other mechanisms requires a detailed and time-consuming safety inspection. I imagine that some researchers would consider working with collaborators in countries with less stringent regulations, setting up wasteful or elaborate schemes to post edited DNA or organisms internationally, or moving overseas.

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.

Gene drives have existing analogues in Nature (eg, the super-Mendelian inheritance of homing endonucleases), which were discovered before they inspired synthetic biologists. It is reasonable to expect synthetic gene drives will have similar

evolutionary pressures as natural gene drives (Burt, 2003). Once they reach fixation in a population, there will be little to no evolutionary pressure to maintain the specific sequence which led to fixation (Goddard & Burt, 1999). This will lead to degeneration of the gene drive and any associated genes by random mutation, leading to complete silencing and less frequently to the reemergence of new gene drives with a different genetic sequence.

We should expect synthetic gene drives will continue to evolve long after they have propagated a 'useful' genetic cargo through a population. This implies that if a contained laboratory experiment is carried out over a long enough time, unintentional release should occur eventually with a finite probability. Similarly, intentionally released gene drives will inevitably evolve and be horizontally transferred to related species. If the time-scale for such events ($<10^6$ years) greatly exceeds the time-scale in which a gene-drive may be useful (say, 10-100 years), and if the transfer of a gene drive to a related species will not result in any undesirable effects, then there should be little safety concern.

However, if it is desirable to limit the entry of synthetic gene drives into the human gene pool, then strict regulations should be made to avoid the creation of gene drives targeting primates or domesticated species that have frequent contact with people.

Goddard, M. R., & Burt, A. (1999). Recurrent invasion and extinction of a selfish gene. *Proceedings of the National Academy of Sciences*, 96(24), 13880-13885.

Burt, A. (2003). Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proceedings of the Royal Society of London B: Biological Sciences*, 270(1518), 921-928.

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.

In the long term, it should become the goal of the OGTR to focus on biological properties. By analogy, we do not assess the safety of chemicals by the process used to synthesise them, but instead by whether a chemical has properties that render it hazardous to human health and whether there are appropriate measures to decrease the risk of accidents. Future biotechnologies will only become more complex and entangled as diverse genetic technologies are invented or repurposed from natural processes of genetic change. As such, it is wasteful and ineffective to focus on process when time and energy should be devoted to considering the biological properties considered safe.