**Submission to the Technical Review of the Gene Technology Regulations: Round 2**

## Introduction

We welcome the opportunity to comment to comment on the Office of the Gene Technology Regulator (OGTR)'s Regulation Impact Statement regarding its proposed changes to the Gene Technology Regulations. However, it is clear that this consultation is a sham and a decision to deregulate these techniques was made well before any public process began. The Regulation Impact Statement is a deeply flawed document that starkly illustrates the extent to which the OGTR has been captured by the biotechnology industry.

The OGTR's claims that new genetic modification (GM techniques) such as CRISPR "do not give rise to any different risks to natural mutations" are scientifically indefensible and reflect the OGTR's over-reliance on advice from scientists with commercial interests in these techniques.

If the OGTR allows these new GM techniques to be deregulated, anyone from amateur biohackers - to industry - to terror groups would be free to use them to genetically modify plants, animals and microbes. Entirely new diseases and poisons could be made. The results could be catastrophic.

The proposed changes represent a veritable coup for the biotech industry. Finally they have found a way to get around the understandable public resistance to GMOs. These proposed changes mean that GM animals, microbes and plants could enter our food chain and our environment with no safety testing and no labelling.

Whilst we appreciate that the OGTR is not responsible for food labelling, our regulator Food Standards Australia New Zealand (FSANZ) will invariably argue for regulatory consistency. If these techniques are deregulated by the OGTR they are also likely to be deregulated by FSANZ.

We are baffled by the following OGTR statement, given that its initial discussion paper mentioned trade issues:

> *"Likewise, no changes will be recommended that relate to topics outside of the current scope of the GT regulations. For example, any issues raised through the consultation process which relate to the regulation of genetically modified food, marketing and trade issues, or the application of new technologies to humans or embryos cannot be considered further through this process."*[1]

Key export markets such as the European Union have yet to make a decision on whether theywill regulate these techniques as GM and have zero tolerance policies for unapproved GMOs. As Markos Kyprianou, EU Commissioner for Health and Consumer Protection puts it:

*"There is no flexibility for unauthorised GMOs - these cannot enter the EU food and feed chain under any circumstances."*[2]

A survey of countries conducted by the Food and Agriculture Organisation (FAO) found that 73% of them have a zero tolerance for unapproved GM varieties.[3] The FAO found that between 2002 and 2012 there had been 200 cases of trade disruptions due to the presence of unapproved GMOs. The majority of the cases happened between 2009-2012, indicating increasing trade problems. Many of these cases cost GM countries millions or even billions of dollars in lost exports.

The OGTR has stated that some of these techniques are currently untraceable. If zero tolerance countries cannot test for these GM techniques, the result is likely to be much broader restrictions on food imports from Australia.

We find it frankly inconceivable that the OGTR or the current government would consider deregulating these techniques with no assessment of the potential trade impacts of doing so. Other countries have taken a more cautious approach to Australia's, with our key agricultural competitor New Zealand recently announcing that it will regulate organisms derived from these techniques as GMOs.[4]

The Australian Gene Technology Act[5] defines gene technology as "any technique for the modification of genes or other genetic material". This would clearly include all new GM techniques unless they were specifically exempted in the Gene Technology Regulations. As the OGTR's discussion paper states:

> *The Explanatory Statement to the 2001 GT Regulations (the 2001 Explanatory Statement) states that "The definition of 'genetically modified organism' in the GT Act was intentionally cast very broadly to ensure that the definition did not become outdated and ineffectual in response to rapidly changing technology."*

That is to say, as gene technologies are developed, the intended default policy setting of the scheme is to regulate all new gene modification technologies and their products.

It is evident that the proposed changes are designed to narrow the scope of the Gene Technology Act so it no longer has the broad scope necessary to ensure that all new GM techniques and their uses are assessed and licensed. This is contrary to the purpose of the Act. The claim that this review is merely technical and has no substantive effect on policy settings is patently incorrect.

We strongly recommend that new GM techniques such as SDN-1 and RNA interference as well as null segregants are regulated as GMOs. The OGTR should dedicate effort to improving the current inadequate system of GMO regulation rather than attempting to limit its scope.

The biotechnology industry argues that these techniques just make small changes to the genome, like mutagenesis. However, unlike mutagenesis - which results in random mutations – these techniques can be used sequentially to make profound, targeted changes to the genome. For example, using SDN1 a bacterial genome could theoretically be re-engineered sequentially to create an organism able to produce the anthrax toxin.

Gene editing techniques such as CRISPR/Cas9 were deemed "weapons of mass destruction and proliferation" in the US Government's 2016 annual worldwide threat assessment report.[6] The OGTR's proposed changes would leave certain applications of these techniques unregulated - despite the present paucity of scientific evidence of their safety.

We are concerned that none of the OGTR's Gene Technology Technical Advisory Committee (GTTAC) abstained from offering advice on the regulation of these new GM techniques even though some of them have clear conflicts of interest. GTTAC's advice has affected the way the OGTR's various options are presented in the paper. We strongly disagree with the GTTAC's assertion that "organisms altered by some site-directed nuclease techniques and oligo-directed mutagenesis are unlikely to pose risks that are different to natural mutations, conventional breeding or mutagenesis."[7] This conclusion is at odds with those drawn by overseas government agencies.[8]

Austrian government agencies are among the few globally to consider the biosafety risks posed by new GM techniques. Their conclusion, over three separate, high-level reviews, is that there is insufficient knowledge of the biosafety risks posed by these techniques to be confident of their safety. On this basis, they argue that products derived from new GM techniques should be regulated in the same way as those created using older GM techniques and require a comprehensive case-by-case risk assessment.[9]

Contrary to the OGTR's assertion, not all of these techniques are new. Restrictions on endonucleases - of which zinc finger nucleases are an example[10] – were already in existence when the Gene Technology Act 2000 was enacted. These techniques are referred to in the 1980 Australian Academy of Science publication *Recombinant DNA: An Australian Perspective.* These techniques are quite clearly GM and need to be regulated in the same way as older GM techniques.

**We therefore oppose the OGTR's proposed deregulation of the new GM techniques.**

Site-directed nucleases (SDNs) rely on the natural DNA repair systems of living organisms, which are far from fully understood. Consequently, the way these techniques work is still hotly contested, even among scientists with relevant expertise and experience. According to a recent review commissioned by the Norwegian Environment and Development Agencies this "poses many uncertainties connected to mode of action as well as potential unintentional effects."[11]

Nowhere in the OGTR's Regulation Impact Statement is there any reference to the potential ecological impacts of the products of the new GM techniques, particularly if gene drives are used to extinguish whole species of organism such as mosquitoes. For instance, the role of mosquitoes as pollinators and as food for migratory birds is well established, but the OGTR does not even consider the enormity of these potential impacts. Given the potentially catastrophic ecological risks posed by gene drives, there should be a moratorium on gene drive research.

The paper also ignores consumer choice. People have a wide range of legitimate reasons for opposing the use of genetically modified organisms (GMOs). These include environmental, health and ethical reasons. Everyone has a right to know if products contain GMOs so that they can avoid them if they want to. While markets are a state issue under the national scheme, deregulation would undermine the capacity of the states to be GM free. This too contradicts the notion that this is simply a technical review – it's much bigger – and requires a far better analysis of all the impacts of deregulation.

It is apparent that the OGTR is under pressure from the biotech industry to adopt a product-based approach to regulation as is used in the USA and Canada, rather than the process-based approach used in the rest of the world and in Australia's Gene Technology Acts. A

product-based approach is unscientific because it ignores the means of production and does not assess the unique risks posed by GMOs.

**Answers to the specific consultation questions**

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

**We support Option 3: amend the GT Regulations with some but not all of the draft amendment proposals.**

We support the repeal of item 1 in Schedule 1. Organisms that have been altered by gene technology should be regulated as GMOs, irrespective of whether any 'foreign nucleic acid' has been introduced.

We strongly oppose the proposed deregulation of site directed nucleases (SDN-1), RNA interference (RNAi) and null segregants. This is completely at odds with the Precautionary Principle embedded in the Gene Technology Act.

The Australian Gene Technology Act[12] defines gene technology as "any technique for the modification of genes or other genetic material". This would clearly include all new GM techniques unless they were specifically exempted in the Gene Technology Regulations.

The Explanatory Statement to the 2001 GT Regulations states that "The definition of 'genetically modified organism' in the GT Act was intentionally cast very broadly to ensure that the definition did not become outdated and ineffectual in response to rapidly changing technology." It was clearly the intent of the regulations to regulate new GM techniques such as SDN-1 and RNAi.

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?**

Yes. However, the language used renders these documents incomprehensible to anyone without a biology degree. Genuine public consultation would mean conveying this information in more accessible language and holding nationwide public consultation events. Instead we have seen a highly technical discussion between 'experts' with serious conflicts of interest behind closed doors. This is completely undemocratic and no way to make a decision with such huge potential ramifications for all Australians.

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

We support the repeal of item 1 in Schedule 1. Organisms that have been altered by gene technology should be regulated as GMOs, irrespective of whether the mutational event involved the introduction of 'foreign nucleic acid' or not.

**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:**

This question clearly illustrates the pro-industry bias of this review. If techniques such as SDN-1 and RNAi as well as null segregants are deregulated financial benefits will accrue to the biotechnology industry. Meanwhile the costs of these techniques in terms of environmental damage, harm to human health and damage to export markets will be borne by society as a whole. This is grossly inequitable.

**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?**

Deregulating SDN-1 and RNAi as well as null segregants is not commensurate with any risks to the health and safety of people and the environment posed by the dealings. The use of all of these techniques poses risks that need to be assessed.

If these techniques are deregulated there will be no monitoring or surveillance. Anyone from amateur biohackers, to industry, to terror groups would be free to use them to genetically modify plants, animals and microbes. Entirely new diseases and poisons could be made. And they could enter our food chain and our environment with no safety testing and no labelling. The risks are enormous and the results could be catastrophic.

All of these techniques result in unpredicted mutations that can result in the production of toxins and allergens.[13] Furthermore, even small changes to the DNA of microbes can result in large differences in pathogenicity. Deregulating the use of these techniques in microbes poses major biosafety risks.

The deregulation of these techniques in animals could lead to a large increase in animal experimentation, raising major ethical issues. The unintended mutations caused by these techniques could pose serious potential animal welfare concerns.

Given the potentially catastrophic risks posed by gene drives, there should be a moratorium on gene drive research.

**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.**

There are a number of features in the options presented that we have concerns with. These include:

**The proposed deregulation of SDN-1**

We oppose the proposed deregulation of GM techniques such CRISPR (SDN-1) when used to make naturally repaired DNA breaks.

SDNs - also referred to as site-specific nucleases (SSN)[14] - use enzymes to cut DNA at specific sites so that genes can be deleted or new genes inserted. The cut DNA is repaired by the

natural DNA repair systems of the plant. There are currently four major classes of SDNs: meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspersed short palindromic repeats (CRISPR)/Cas9 reagents.[15]

- **Zinc-finger nucleases (ZFN)**
    - This technique involves the use of an engineered enzyme to introduce site-specific mutations into the plant genome. Depending on the type of ZFN technology deployed, mutations can either be restricted to one or a few nucleotides or involve the insertion of a new piece of DNA;
- **Transcription activator-like nucleases (TALEN)**
    - These enzymes are similar in structure in ZFNs but have longer DNA binding sites;[16]
- **Meganucleases/homing endonucleases**
    - These are naturally occurring DNA cutting enzymes that have been isolated from a range of organisms including yeast and green algae;[17]
- **CRISPR/Cas9-Nucleases**
    - These are synthetic enzymes developed from a bacterial enzyme that is part of the bacteria's immune system that is used to recognise and destroy foreign DNA;[18]
    - This technique has only been developed in the last couple of years. Scientists have been excited by its versatility leading many to inaccurately characterise it as a 'precise gene editing tool'.[19]

SDN-1 cuts the DNA without the presence of a donor DNA repair template. This can result in site-specific random mutations or deletions but can also result in the deletion of whole genes and even parts of chromosomes. It can also cause genomic inversions or translocations.[20]

The ways in which DNA double stand breaks are repaired and the potential consequences of misrepair are still not fully understood.[21] A review commissioned by the Norwegian Government observed that our understanding of these mechanisms is still in its infancy and that the majority of the studies have been done on mammalian cells not plant, microbial or other animal cells.[22]

The Austrian Environment Agency's recent review found that SDNs can result in a number of possible unexpected effects. However, because of the current lack of knowledge regarding the mechanisms involved in these techniques, significant uncertainties are associated with an assessment of unintended effects.[23]

And the review commissioned by the Norwegian Government found that:

> *"There are several factors that influence both DNA binding and DNA repair, unfortunately they are to a large extent not fully understood. The lack of mechanistic understanding is a severe limitation for identifying potential hazards from SDNs and more research in this field is greatly recommended. Identifying unintentional effects in a system which is not fully understood becomes very difficult."*[24]

According to the Austrian Environmental Agency[25] unexpected effects caused by SDNs can result from:

- Unexpected mutations in genes sharing similar DNA sequences to the target gene;
- Knock-out mutations that result in fusion genes which could create potentially toxic fusion proteins;
- Unintended mutations as a result of the methods used to introduce SDNs into the target cells. This usually involves older GM techniques such as *Agrobacterium*-mediated transformation or bombardment using a gene gun;
- Changes in gene expression;
- Genes introduced using SDN-3 techniques behaving differently when inserted into different parts of the genome.

*Off-target effects*

One of the main concerns with these techniques is unexpected mutations due to the SDNs cutting DNA outside the target site. This has been observed for the ZFN, TALEN and CRISPR techniques.[26] Agapito-Tenfen and Wikmark (2015) observe that small deletions can cause gene knockout and some mutations. While these may not lead to easily detectable changes they can still trigger safety concerns. Furthermore, it is unsafe to assume that these changes will not be heritable.[27]

The Austrian Environment Agency's review also found that ZFNs result in significant unexpected mutations.[28] This is also an important problem for the TALEN technique and, according to another recent review, can result in severe side effects.[29] Fine *et al.* (2014) highlighted that indentifying off-target mutations for ZFN and TALEN is a daunting task because of the size of genomes and the large number of potential mutation sites to examine.[30]

Studies suggest that CRISPR results in even more off-target mutations than ZFN and TALENs.[31]For example, a recent study found that CRISPR/Cas9 can result in hundreds of unexpected mutations.[32]

Agapito-Tenfen and Wikmark (2015) conclude that off-target mutations occur with all SDN techniques and it is impossible to predict what these might be,[33] therefore:

> *"comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[34]

CRISPR has only been used for genetic engineering for the past 5 years. Reviews commissioned by the Austrian and Norwegian governments concluded that not enough is known about the risks posed by new GM techniques such as CRISPR. They recommended that products derived from these techniques require comprehensive case-by-case risk assessments.

Deregulating techniques such as CRISPR, given the knowledge gaps that exist around the risks they pose is completely at odds with the Precautionary Principle embedded in the Gene Technology Act.

*Mutations created using these techniques are fundamentally different to natural mutations*

The OGTR's claims that new genetic modification (GM techniques) such as CRISPR "do not give rise to any different risks to natural mutations" are scientifically indefensible and reflect the OGTR's over-reliance on advice from scientists with commercial interests in these

techniques.

Your argument that these mutations could occur naturally and therefore don't need to be regulated is disingenuous, since the natural mutation rate is extremely low. One plant study found that the probability of any letter of the genome changing in a single generation is about one in 140 million.In contrast these new GM techniques can cause hundreds of unwanted mutations in some organisms.[35]

Not all natural mutations are "safe" and most of them - if they would occur at all - are not used for straightforward and rapid commercial development and use.

Furthermore, no good criteria are available to distinguish risky mutations from less risky ones. The size or specificity of the genetic change has relatively little relevance to the extent of change in the organism and consequently to the risk that it poses to the environment or food safety.

*Mutagenesis techniques do not have a 'history of safe use'*

Your argument that these techniques create similar results to chemical and radiation mutagenesis which have a history of safe use does not stand up to scrutiny. Neither of these techniques have been safely used in animals or microbes. Chemical and radiation mutagenesis also typically result in small point mutations – whereas SDN-1 results in DNA double strand breaks.

Unlike chemical and radiation mutagenesis which increase the rate of random mutation, all of these techniques can be used sequentially to make dramatic changes to the genome.

Chemical and radiation mutagenesis could also result in the production of allergens and toxins and should be regulated. Arguing that new techniques such as CRISPR should be deregulated because of the Government's failure to regulate other potentially risky techniques sets a dangerous precedent.

*All of these techniques rely on older GM methods with the same associated risks*

All of these techniques rely on older GM methods such as protoplast creation, biolistics, electroporation,tissue culture, and *Agrobacterium*-mediated gene transfer. These can all cause unexpected mutations that would be extremely unlikely to occur in nature. This is why organisms produced using them need to be assessed for safety.[36]

All of the new GM techniques can also result in the accidental incorporation of bacterial or synthetic DNA into the chromosome. With no regulation, these unexpected effects won't be looked for.[37]

*Detectability*

Your claim that organisms modified using these techniques would be indistinguishable from natural organisms and so regulation would be unenforceable is nonsensical. Existing SDN-1 products such non-browning mushrooms are patented – requiring full molecular

characterisation and enabling traceability.

Claims that GMOs produced using SDN-1 are not detectable only consider the current unequivocal signatures of GMOs obtained through transgenesis. These signatures of course help using "cheap" and "rapid" detection methods but there are a number of techniques that can be used to identify organisms produced using SDN-1.[38]

The development of further protocols (including advances in the robustness of whole genome sequencing) and techniques may allow for better, cheaper and more reliable detection of small changes (e.g. one base pair changes) in genome edited organisms. These include 'BATCH-GE', a bioinformatics tool for batch analysis of DNA sequence data and spectroscopy methods for differentiating between genome-edited and conventionally bred plant varieties.[39]

It is evident that advances in detection technologies are needed, not only for genome-edited organisms, but for other techniques such as RNAi. Already networks of laboratories exist that coordinate and develop techniques to detect GMOs. In Europe, there is the European Network of GMO Laboratories (ENGL). ENGL could play a role in the discussion on detectability of new organisms generated with new techniques, if it were commissioned to do so. There just needs to be the political will to develop suitable detection technologies.

Even if claims that such changes could not be detected were true, not having an analytical control / enforcement method for tracing any product is not an acceptable legal argument, since numerous products in supply chains are only traced by documentary traceability tools. These include free range, organic, fair trade and products from specific countries of origin.

As the regulator of these techniques the OGTR should mandate that developers supply a detection test. Releasing untested GMOs into the environment and our food chain without a detection test is a recipe for disaster and we find it frankly astonishing that the OGTR is even considering this.

**Null segregants**

We oppose the deregulation of 'null segregants' – the offspring of GMOs which supposedly no longer contain any GM DNA. This is an assumption that needs to be tested via regulation involving full molecular characterisation. The definition of a GMO in Australia should include organisms derived from GMOs, or those that include temporal GMOs, as is the case in the EU.

**RNA interference and gene silencing**

We oppose the proposed deregulation of RNA interference and gene silencing – as recommended by Bayer, Nuseed and AusBiotech. Induced changes to genomic DNA methylation are heritable and should be regulated. The Australian Gene Technology Act defines gene technology as "any technique for the modification of genes or other genetic material". RNA is clearly genetic material and this definition clearly includes RNA interference and gene silencing.

The US Environmental Protection Agency *White Paper on RNAi Technology as a Pesticide*[40] summarises the well-founded concerns that non-target organism could be adversely

affected if RNA interference is used as a crop protectant against insect pests. This is the case whether the RNAi is topically applied, or produced via a GMO. Therefore, it is essential that all applications of RNAi within the environment undergo a risk assessment (i.e. are regulated).[41] Given its expertise in the risk assessment of GMOs we view the OGTR as the appropriate regulator to conduct this risk assessment rather than the APVMA.

## Specific technical comments

We oppose the addition of Section 13(3A). The safety of GM microorganisms cannot be established from that of the parent, non-modified microorganism. Similarly we oppose the addition of Section 13(3)(b). Allowing a written authorisation for transport and/or disposal of GMOs outside the guideline requirements in s 13(3)(a) is neither justified, nor are any standards imposed as part of that provision.

We oppose the new reporting requirements for NLRDs (s 13C), which permits the regulator to be notified in an annual report rather than at the time the person or accredited organisation has been given a record of assessment by the IBC. Weakening reporting requirements weakens the capacity to monitor, audit and enforce the regulations. We note too that this is not a technical amendment.

Similarly, we oppose the amendment of s. 39 to weaken the reporting requirements for NLRD, in particular eliminating the requirement to describe and provide information regarding the GM product.

We oppose the inclusion of any RNA techniques as not being gene technology in Schedule 1A.

We oppose the inclusion of Schedule 1B (and regulation 4A). It is legally unnecessary and sloppy to define both the techniques that are GM and those that aren't GM, when the current definition provides a far clearer and cleaner method of determining what is GM. Schedule 1B is narrower than the definition in s. 10 of the Act and creates some serious uncertainties:

- Are techniques not listed in either schedule GM or not GM?
- What is the relationship between the definition in s. 10 of the Act and the definitional limitations in Schedule 1B?
- Is either list exclusive?
- Who decides whether a product or organism is GM and by what process?
- And are those decisions reviewable?

Once again, this is not a technical amendment but a substantive weakening of the Act and its current definition of GM.

We support the repeal of item 1 in Schedule 1. Organisms that have been altered by gene technology should be regulated as GMOs, irrespective of whether any 'foreign nucleic acid' has been introduced.

We oppose the addition of items 4, 8, 9, 10 and 11 to Schedule 1. These organisms are quite clearly genetically modified.

We oppose the addition of Section 2.2(2) to Schedule 3. The safety of GM microorganisms cannot be established from that of the parent, non-modified microorganism.

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[1] OGTR (2017)*Updating Gene Technology Regulation in Australia: Regulation Impact Statement for consultation*, p. 8

[2] European Commission(2006)*GM FOODS - Commission requires certification of US rice exports to stop unauthorised GMO entering the EU: Press Release (IP/06/1120)*,23 August 2006, http://www.reading.ac.uk/foodlaw/news/eu-06080.htm

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[4]Smith, N. (2016) *GMO regulations clarified*, 5/4/16, https://www.beehive.govt.nz/release/gmo-regulations-clarified-0

[5] Gene Technology Act 2000, p.6

[6]Regalado, A. (2016) Top U.S. Intelligence Official Calls Gene Editing a WMD Threat, *MIT Technology Review*, 9/2/16, https://www.technologyreview.com/s/600774/top-us-intelligence-official-calls-gene-editing-a-wmd-threat/

[7] OGTR (2016) Discussion paper: Options for regulating new technologies

[8]See e.g.: Agapito-Tenfen, S.G. &Wikmark, O-G (2015) *Current status of emerging technologies for plant breeding: Biosafety and knowledge gaps of site directed nucleases and oligonucleotide-directed mutagenesis*, p. 5; Austrian Agency for Health and Food Safety (AGES) (2012) *Cisgenesis. A report on the practical consequences of the application of novel techniques in plant breeding*. Report for the Austrian Federal Ministry of Health; Austrian Agency for Health and Food Safety (AGES) (2013) *New plant breeding techniques. RNA-dependent methylation, Reverse breeding, Grafting*. Report for the Austrian Federal Ministry of Health; Eckerstorfer, M., Miklau, M. &Gaugitsch, H. (2014) *New plant breeding techniques: risks associated with their application*, Austrian Environment Agency, http://www.ekah.admin.ch/fileadmin/ekah-dateien/New_Plant_Breeding_Techniques_UBA_Vienna_2014_2.pdf

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[11]Agapito-Tenfen, S.G. &Wikmark, O-G (2015) p. 5

[12] Gene Technology Act 2000, p.6

[13] ENSSER (2017) ENSSER statement on new genetic modification techniques, https://ensser.org/topics/increasing-public-information/ngmt-statement/

[14]*Ibid.,*p. 22

[15]*Ibid.,*p. 8; For a fuller discussion of these techniques see Eckerstorfer, M. *et al.* (2014) p. 22-19

[16]Eckerstorfer, M. *et al.* (2014) p. 23

[17]Eckerstorfer, M. *et al.* (2014) p. 24

[18]Eckerstorfer, M. *et al.* (2014) p. 24

[19] See e.g., 'Our superhuman future is just a few edits away', *New Scientist,* 26/9/15, p. 28-30,

[20]Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 16-17

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[22]Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 22

[23]Eckerstorfer, M. *et al.* (2014) p. 25

[24]Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 4

[25]Eckerstorfer, M. *et al.* (2014) pp. 25-29

[26]Agapito-Tenfen, S.G. &Wikmark, O-G (2015), pp. 18-21; Eckerstorfer, M. *et al.* (2014) pp. 25-29.

[27]*Ibid.,*p.22

[28]Eckerstorfer, M. *et al.* (2014) p. 26

[29]Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 20

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[32] Han, A.P. (2015) New Sequencing Methods Reveal Off-Target Effects of CRISPR/Cas9, https://www.genomeweb.com/sequencing-technology/new-sequencing-methods-reveal-target-effects-crisprcas9

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