Australian Government

Department of Health

Office of the Gene Technology Regulator

MINUTES OF THE
GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE
23 November 2016 Meeting

About these Minutes

These minutes are intended to summarise discussion during the 50th meeting of the Gene Technology Technical Advisory Committee (GTTAC), held on 23 November 2016. They reflect key elements of the discussion, outcomes, matters agreed and actions arising, and are not intended to be a verbatim record of the meeting.

Attendance

Members

- Professor John Rasko AO (GTTAC Chair)
- A/Prof Jason Able
- E/Prof Craig Atkins
- Prof Ross Barnard
- Prof Jacqueline Batley
- Prof Gabrielle Belz
- Dr Graham Bonnett
- Ms Laura Fell
- Prof Ian Godwin
- A/Prof John Hayball
- Dr Rodney Mahon
- Dr Michael Michael
- Dr Gabrielle O'Sullivan
- Prof Marie Ranson
- Dr Kelly Shaw
- A/Prof Jason Smythe
- Dr Diane Webster
- Prof Paul Young

Apologies

- Prof Kevin Smith

Guests

- Dr Raj Bhula (Gene Technology Regulator)
- Dr Michael Dornbusch (GTTAC Secretary)

Presenters

- Dr Eong Ollis
- Dr Helen Holt
- Dr Vijay Mareddy
- Dr Brian Weir
- Dr Louisa Matthew

Secretariat

- Mr Greg Barber
- Dr Gillian Colebatch
- Mr Dimitri Kun

The meeting commenced at 09:15am (AEST)

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Agenda Item 10. Review of the Gene Technology Regulations 2001

The Chair invited Dr Louisa Matthew to provide members with an update on progress of the Regulator's technical review of the Gene Technology Regulations 2001 (the Regulations), and to seek advice on gene drives and RNA interference.

Specifically, advice was sought by the Regulator from GTTAC on the following:

1. Could contained laboratory research on GM gene drive organisms pose different risks to human health and safety and the environment to other contained research with GMOs? If so,

- what are these risks?
- what evidence is available to support the assessment of these risks?
- how could these risks be managed?

2. Please identify newly developing RNA interference (RNAi) techniques and applications you are aware of, including details of relevant technical publications where possible.

The Chair asked whether members were aware of any new RNAi techniques. Dr Michael Michael noted that using Cas9 to chop up RNA was a relatively new way of achieving similar results to RNAi techniques. He added that modified Cas9 had been used to bind GFP to RNA molecules so that they could be tracked around cells. Members referred to publications in PNAS[3] and Nature[4] on Cas9-tagetting of RNA and Prof Paul Young sent them to the OGTR via email.

The Chair recalled a recent publication involving a system similar to CRISPR/Cas9, and Prof Barnard added that there were at least 6 systems from different organisms already identified.

Moving to the question on gene drives, the Chair commented that there is a substantive difference between this technology and other biotechnology. Dr Bonnett sought clarification on whether the

[3] Price et al (2015) Cas9-mediated targeting of viral RNA in eukaryotic cells. *PNAS* 112(19):6164-9
[4] O'Connell et al (2014) Programmable RNA recognition and cleavage by CRISPR/Cas9. *Nature* 516(7530): 263-6

advice sought related to risks if a GMO with a gene drive is released, or if it stays in containment. Dr Kelly Shaw noted that the potential effects of gene drives are currently theoretical and queried whether the questions could be answered in the absence of evidence or data.

Prof Barnard considered the questions that need to be addressed are whether the current containment rules are adequate, and whether the GMO could be controlled if it escaped containment. He suggested that although the containment regulations are in place, if an organism with a gene drive was to escape containment, it could be very difficult to retrieve it. Prof Smythe agreed that current containment requirements are likely to be adequate for GMOs with a gene drive, but added that the assessment would need to look at the particular trait.

Dr O'Sullivan noted that some NLRDs can be undertaken in a PC1 facility unless the modification confers an advantage, and queried whether gene drives could sometimes confer a disadvantage. Dr Matthew clarified that any GMO with a functional gene drive is considered to have an advantage, and a minimum containment level of PC2 is required. Dr O'Sullivan commented that this may not be clear to researchers or IBCs.

> *Secretariat note:* Following the meeting, the OGTR published a guidance document for IBCs on regulatory requirements for contained research with GMOs containing engineered gene drives: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/ibc-1

Prof Ross Barnard asked whether a dealing with a GMO containing a gene drive could be an exempt dealing. Mr Will Tucker responded that it is possible *Caenorhabditis elegans* with a GM gene drive could be exempt, but not any plants or animals.

> *Secretariat note:* Mr Tucker subsequently clarified that *C. elegans* with a functional gene drive should be excluded from exempt dealings, as the relevant clause (Schedule 2, Part 1, Item 2) excludes modifications which provide an advantage.

The Chair proposed that a GM gene drive organism could pose different risks to human health and the environment than other GMOs if it escaped containment. A/Prof Smythe commented that a PC2 facility is considered adequate for containment of most GM insects and plants, so these organisms can only escape containment through an unintentional or release or by someone deliberately not following containment requirements. A/Prof Smythe suggested that gene drive organisms would not pose different risks within PC2 facilities but agreed with the Chair that they may do so if they escaped containment.

Prof Ian Godwin considered it would be difficult to propose adequate limits and controls for a limited and controlled release of a GM gene drive organism. Dr Bonnett noted that some modifications included safeguards to allow appropriate levels of control of the spread of the GMO.

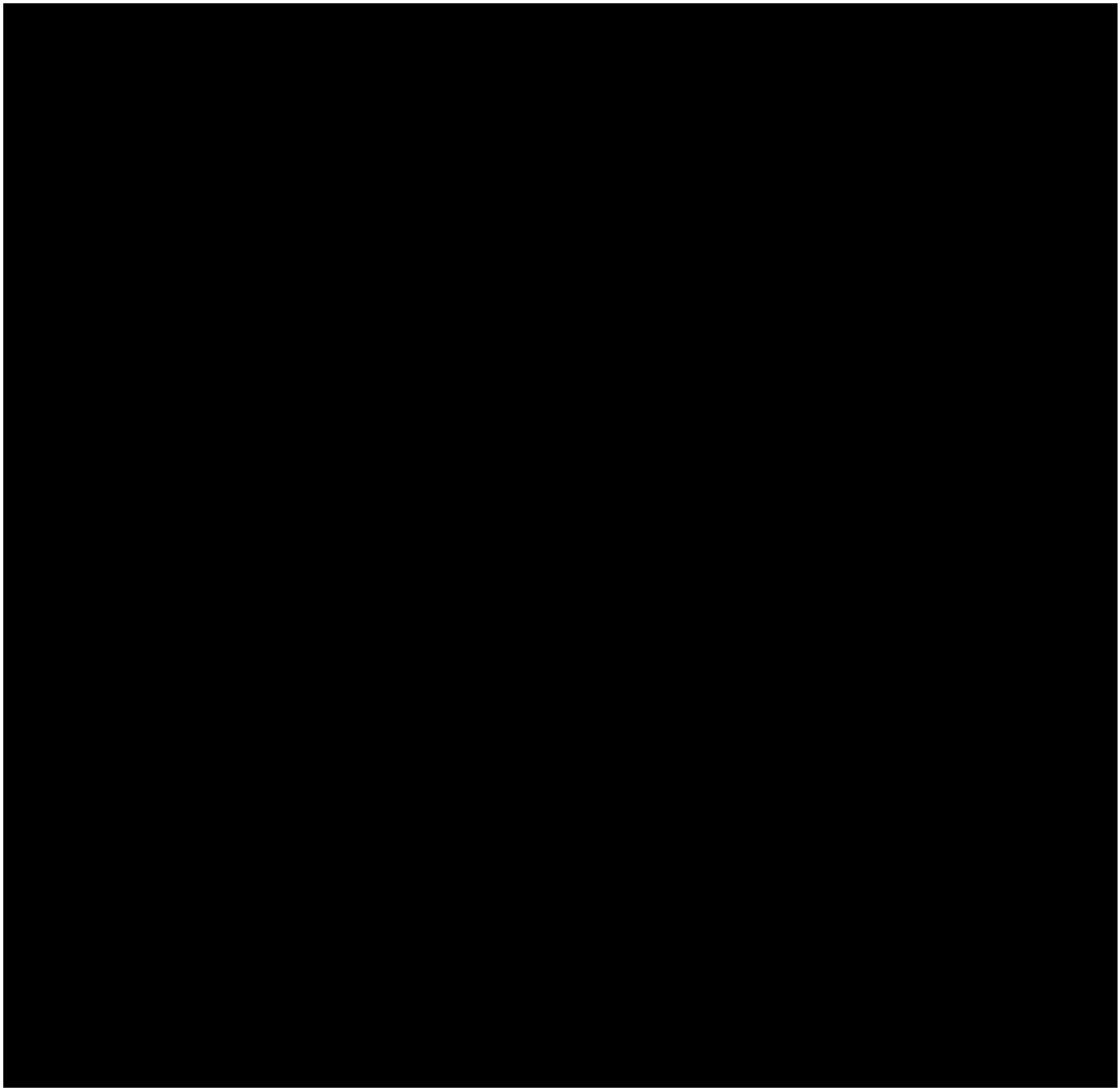
Leaving aside the question of what controls or containment level might be needed, the Chair asked if members agreed that GMOs with gene drives could pose different risks than other GMOs, and the committee confirmed agreement with a show of hands.

The Chair asked members to specify the risks posed by GM gene drive organisms. Dr Bonnett suggested that the main risk is harm to the environment, including destruction of a species as the most extreme consequence. Prof Kevin Smith observed that the possible effects of gene drives on populations were theoretical and there is no evidence that a population could be destroyed. Prof Barnard commented that possible effects have been extrapolated from an understanding of the mechanisms. Prof Godwin considered that the technique may not work as well as predicted theoretically. The Chair proposed the OGTR keeps watching the development of these techniques and emerging evidence of how effective they are.

Moving to the question of risk management, the Chair noted that well considered regulations and guidelines would allow any risks to be managed. Prof Barnard commented that there are already structured regulations with different categories of dealings requiring different levels of containment.

Resolution:

- Publications on Cas9-tagetting of RNA were provided to the OGTR
- Depending upon the cargo and its effects, gene drive containing organisms may pose different risks if accidentally released from appropriate containment
    - Risks include risks to people and the environment, including the potential to adversely impact on populations/ecology
    - Evidence to support assessment of these risks is currently mostly theoretical; the Regulator should keep a watching brief on emerging data and evidence
    - Risks could be managed by giving further consideration to containment measures, guidelines and appropriate regulation.



COLEBATCH, Gillian

From: Paul Young [redacted]
Sent: Wednesday, 23 November 2016 14:01
To: ogtrcommittees
Subject: Re: Cas9 RNA editing paper for consideration [SEC=No Protective Marking]
Attachments: PNAS-2015-Price-6164-9.pdf

Australian Government

Department of Health

Office of the Gene Technology Regulator

MINUTES OF THE
GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE
6 June 2016 Meeting

About these Minutes

These minutes are intended to summarise discussion during the Gene Technology Technical Advisory Committee (GTTAC) 6 June 2016 meeting. They reflect key elements of the discussion, outcomes, matters agreed and actions arising, and are not intended to be a verbatim record of the meeting.

Attendance

Members
- Professor John Rasko AO (GTTAC Chair)
- A/Prof Jason Able
- E/Prof Craig Atkins
- Prof Ross Barnard
- Prof Gabrielle Belz
- Dr Graham Bonnett
- Ms Laura Fell
- Prof Ian Godwin
- A/Prof John Hayball
- Dr Rodney Mahon
- Dr Michael Michael
- Dr Gabrielle O'Sullivan
- Prof Marie Ranson
- Prof Kevin Smith
- A/Prof Jason Smythe
- Dr Diane Webster
- Prof Paul Young

Apologies
- Prof Jacqueline Batley
- Dr Kelly Shaw

Guests
- Dr Jane Cook (A/g Gene Technology Regulator)
- Dr Michael Dornbusch (GTTAC Secretary)
- Ms Judy Jones (Chair of the Gene Technology Ethics and Community Consultative Committee)

Presenters
- Dr Louisa Matthew
- Dr Dennis Dowhan
- Dr Peter Thygesen
- Dr Anne-Sophie Dielen

Secretariat
- Mr Greg Barber
- Dr Gillian Colebatch
- Mr Dimitri Kun
- Ms Lill Sclater

The meeting commenced at 09:30am (AEST)

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Agenda Item 4. New Technologies

Dr Louisa Matthew gave a presentation and sought GTTAC's advice on the technical aspects of new technologies, including site-directed nuclease (SDN) techniques[1], to inform the Regulator's technical review of the Gene Technology Regulations 2001 (the Regulations). The Chair thanked Dr Matthew for providing a very clear presentation of a complex topic.

The Chair reminded members that the discussion paper they had been provided cannot be circulated until it is made public, which will be after the outcome of the federal election is known.

The following five questions were put to the committee:

1. Are the risks posed by organisms altered by non-homologous end joining to repair DNA cleavage (i.e. SDN-1) any different to naturally mutated organisms?
2. Does SDN-2 or oligo-directed mutagenesis (ODM) pose any risks that are different to natural mutations, conventional breeding or mutagenesis?
3. Could successive rounds of modification using SDN-2 or ODM give rise to any new risks?
4. Do the potential off-target effects of SDNs or ODM pose different risks to the intended effects of these techniques?
5. What is the evidence base available to support the assessment of the above risks?

Members queried the positions of other governments and regulatory authorities regarding the risks to the health and safety of people and the environment posed by new technologies. Dr Matthew advised that there was a lot of discussion going on internationally but no clear decisions had been made. She informed members that in the United States, Cibus' Rapid Trait Development System™ is not regulated as gene technology, but a review of the US regulatory scheme is underway. Dr Graham Bonnett commented that the current regulatory scheme in the US has a different trigger than in Australia.

The Chair suggested that early discussions around human clinical trials, antisense techniques, oligonucleotides as therapeutics and other techniques when they emerged may provide some precedent for how new techniques are considered. He commented that Australia's gene technology regulatory scheme has worked well to date but does need reviewing to clarify the regulatory status of new technologies. Prof Paul Young referred to a very recent publication on an RNA-targeting CRISPR system, and asked whether such a new tool could be also considered in the review of the Regulations.

Prof Ross Barnard and Dr Matthew agreed that ODM was not a new technique, rather it was in use when the Act came into effect. Dr Matthew added that clarity around its regulatory capture would still be useful. Prof Barnard observed that off-target effects were neither new nor unique to the new technologies, for example using restriction enzymes, or some of the other longstanding, routinely used mutagenesis or cloning methods, can also result in off-target effects. Prof Young added that all changes made by chemical and radiation-induced mutagenesis were untargeted. Prof Ian Godwin suggested that off-target effects from new technologies may be less likely because the changes are so targeted, but the presence of multi-gene families might mean the effect is greater.

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1 Site-directed nuclease (SDN) techniques:

- SDN-1: non-homologous end joining repairs DNA cleavage, which can result in random insertions, deletions and substitutions, often of only a few nucleotides.
- SDN-2: homology-directed repair of DNA cleavage is guided by a supplied template, incorporating changes to one or a few nucleotides.
- SDN-3: homology-directed repair of DNA cleavage is guided by a supplied template, inserting a new gene or genetic element.

Dr Bonnett clarified that SDN-1 can be used to produce sequence deletions, which Dr Matthew confirmed. Prof Godwin observed that his experiments in sorghum using SDN-1 produced a range of sequence changes, including variations in the number of nucleotides deleted.

The Chair referred to the first question being asked and Prof Marie Ranson, Prof Barnard and Prof Godwin agreed that the risks posed by organisms altered by SDN-1 are unlikely to be any different to naturally mutated organisms. Dr Michael suggested that the answer might be different if human embryos are being considered. Dr Matthew advised that, in some cases, genetic modification of humans may be regulated under the Act, but the NHMRC also regulates research involving human embryos and human cloning.

Addressing Question 2, members discussed what types of sequence changes could be achieved using SDN-2. Dr Matthew advised that generally modifying one or a few nucleotides were associated with use of SDN-2, and larger changes were generally associated with use of SDN-3. Dr Gabrielle O'Sullivan noted that the size of the change is not always important, since even changing a single amino acid has been shown to increase the pathogenicity of some organisms.

The Chair invited Ms Fell to comment. Ms Fell suggested that not everyone will distinguish these techniques from traditional genetic modification techniques, and the Chair and Dr Dornbusch agreed. Dr Dornbush informed members that public consultation will take place after this technical input and some indication of public perceptions of these technologies may be gauged as a part of the consultation process.

The Chair asked members whether the risks from SDN-2 or ODM are different to natural mutations, conventional breeding or mutagenesis. A/Prof Jason Smythe considered that risks are unlikely to be different when the techniques are used once (as in Question 2), but may be different when they are used to make successive rounds of modifications (as in Question 3).

Prof Kevin Smith commented that the techniques suddenly becoming accessible is another issue additional to the technical risks being discussed today. The Chair commented that these new technologies do not result in any changes that were not achievable from older, more expensive techniques – the difference is that everyone can access them. A/Prof Smythe suggested a minor difference is that the new technologies have the potential to deliver more specific, targeted changes.

Referring to Question 3, Dr Diane Webster asked whether successive rounds of modifications in one gene using SDN-2 could result in the sort of change that SDN-3 causes, and A/Prof Smythe said that it could. Prof Smith commented that using SDN-2 at a number of different sites in the genome would be similar to multiple rounds of mutagenesis, but that if the same site was targeted then the result may be like SDN-3 or inserting a gene. Dr Dornbusch summarised that therefore successive rounds of SDN-2 may pose risks similar to inserting a gene.

The Chair referred to Question 4 and suggested that the potential off-target effects of SDNs or ODM do pose risks different to the intended effects, and members agreed. Moving to Question 5, the Chair commented that the evidence base for new technologies is large and rapidly growing. Dr Dornbusch requested that members with any relevant references forward them to the OGTR. The Chair added that Australia has a number of experts that could be called on, including Prof Ryan Lister, Dr Marco Herold, Prof Peter Waterhouse, and Prof Paul Thomas, who all have specific experience with this technology.

Prof Godwin raised a concern that changes made now to the Regulations may not keep up with the rapidly evolving technology. Dr Bonnett commented that the approach of other regulators such as FSANZ may complicate the issue. Dr Matthew responded that FSANZ has a different focus so their approach does not necessarily need to match the OGTR's. That aside, the OGTR is in regular

contact with FSANZ on this topic and the two agencies keep each other up to date with developments.

The Chair reminded members that the committee's focus is on the science, and it is not a question for GTTAC how this could be legislated. Dr Matthew advised that the next steps will be public consultation on options for updating and improving the Regulations in relation to new technologies.

GTTAC provided the following advice to the Regulator:

Resolutions:

1. Risks posed by organisms altered by SDN-1 are unlikely to be different to naturally mutated organisms.
2. SDN-2 and oligo-directed mutagenesis are unlikely to pose risks that are different to natural mutations, conventional breeding or mutagenesis.
3. Successive rounds of modifications using SDN-2 and oligo-directed mutagenesis may pose risks similar to inserting new genes or SDN-3.
4. Off target effects do pose risks different to the intended effects.
5. Members recommended some experts and will send relevant evidence.

[redacted]

COLEBATCH, Gillian

From: Paul Young [redacted]
Sent: Wednesday, 23 November 2016 14:15
To: ogtrcommittees
Subject: Re: Cas9 RNA editing paper for consideration [SEC=No Protective Marking]
Attachments: O-Connell_et_al-2014-Nature.pdf

…and this one

From: Paul Young [redacted]
Date: Wednesday, 23 November 2016 1:00 pm
To: ogtrcommittees <ogtrcommittees@health.gov.au>
Subject: Re: Cas9 RNA editing paper for consideration

Australian Government

Department of Health

Office of the Gene Technology Regulator

MINUTES OF THE

GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE

Meeting 47 – 8 April 2015

AMA House, Canberra

About these Minutes

These minutes are intended to summarise discussion during the Gene Technology Technical Advisory Committee (GTTAC) meeting of 8 April 2015. They reflect key elements of the discussion, the outcomes, matters agreed and actions arising. They are not intended to be a verbatim record of the meeting.

Attendance

Members:

- Professor John Rasko AO (GTTAC Chair)
- Dr Jason Able
- Professor Craig Atkins
- Professor Ross Barnard
- Professor Jacqueline Batley
- Professor Gabrielle Belz
- Dr Graham Bonnett
- Ms Laura Fell
- Professor Ian Godwin
- A/Prof John Hayball
- Dr Rodney Mahon
- Dr Michael Michael
- Dr Gabrielle O'Sullivan
- A/Prof Marie Ranson
- Dr Kelly Shaw
- Professor Kevin Smith
- A/Prof Jason Smythe
- Dr Diane Webster

Apologies:

- Professor Paul Young

Guests:

- Dr Robyn Cleland (A/g Gene Technology Regulator)
- Dr Paul Keese (A/g GTTAC Secretary)

Presenters:

- Dr Dennis Dowhan
- Dr Sarah Weisman
- Dr Vijay Mareddy
- Dr Markus Koeck
- Dr Brian Weir
- Dr Louisa Matthew

Observers:

- Dr Heidi Mitchell
- Mr Will Tucker

Secretariat:

- Dr Peter Thygesen
- Dr Gillian Colebatch
- Mr Dimitri Kun

The meeting commenced at 08:50 am

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Agenda Item 10. New technologies

The Chair welcomed Dr Louisa Matthew, who updated members on the issue of regulatory coverage of organisms generated with new technologies. The following key issues were raised:

- The scope of Australian regulation of genetically modified organisms (GMOs) is determined by the legal definitions in the *Gene Technology Act 2000* (the GT Act) and the Gene Technology Regulations 2001 (the Regulations).
- The Regulations were drafted prior to a range of new techniques being contemplated. In response to queries from the regulated community, the Regulator is considering whether organisms generated with particular new technologies are captured or excluded by the regulatory scheme.
- The Regulator is preparing to review the Regulations to ensure regulation of these organisms is commensurate with risk and to provide clarity about their capture.

GTTAC was asked to discuss the following questions:

- Does GTTAC support a review of the Regulations?
- What technical considerations should inform the review?

The Chair asked what the timeframe for reviewing the Regulations would be, noting the context of rapidly evolving technology. The Regulator answered that the OGTR is hoping that it will not take as long as the previous review, which is partly why this review will focus on a single issue, albeit a complicated one. The aim is one year but this may be optimistic, and will depend on obtaining policy approval. The Chair asked whether that would include three months for consultation, and the Regulator replied that it is not yet clear. She added the Intergovernmental Gene Technology Agreement required the Act to be reviewed every 5 years, which would mean the next review may occur in 2016. If so, the reviews of the Act and Regulations may converge. The Regulator advised

that the next step regarding a review of the Regulations would be to develop sensible principles to take forward.

Dr Smythe asked whether there was an internal process that could be done before formal approval to undertake a review was sought. The Regulator commented that the OGTR has already been looking at this issue, including development of a consistent approach for providing guidance to queries regarding regulation of new technologies, and to provide clarity both to applicants and the OGTR. This is essentially a definitional issue which can only be changed through the legislation.

Dr Smythe asked if the Regulator has any discretion to define what is a GMO. The Regulator replied that it is more of a legal question and we can only make decisions within the scope of the legislation. Operationally, we are trying to make consistent case-by-case decisions.

The Chair referred to the first discussion question and asked if members supported a review of the Regulations being undertaken. Members indicated unanimous support for a review of the Regulations.

Professor Barnard asked what was the status of an organism made with CRISPR technology that removed DNA. He suggested that it is the product that should be looked at, and that process based regulation in Europe was problematic. Dr Matthew commented that at this stage the OGTR is considering a review of the exclusions in the regulations rather than a review of the definitions in the Act. The Chair noted that the Australian regulatory scheme for GMOs is very robust and gross changes to the legislation are not needed.

Professor Godwin suggested it would be difficult to distinguish sorghum developed with CRISPR from naturally occurring mutants. The Regulator commented that this is not a new issue for the OGTR as naturally occurring deletions can also be similar to deletions created with gene technology. The Chair added that a modification not being detectable may not mean it is not a GMO, and there would be a paper trail documenting its development. The Regulator added that this becomes a compliance issue.

Dr Bonnett made the distinction between intending to make a specific change to the genome versus unintentionally achieving the same change using mutagenesis, which is not regulated. The Chair agreed and suggested that using gene technology to make deliberate changes should be regulated.

Dr Michael noted that RNAi techniques can also cause issues for IBCs, and suggested they could be excluded if no change to the DNA occurs. Dr O'Sullivan commented that the intention should be broad enough capture to allow the Regulator to assess the risks appropriately. She suggested that some changes to the definitions in Schedule 1 and 1A of the Regulations could help remove ambiguity between them; such as replacement of the term 'foreign nucleic acid' with 'gene technology' in item 1 of Schedule 1. She noted that some commentators from the field of ethics, such as Nuffield Council[2], consider that genome editing techniques give rise to concerns because of their potential to increase the scope and scale of genetic modification due to their greater applicability and precision.

Dr Thygesen reminded members that the gene technology regulatory scheme is precautionary and based on risk. He added that any amendments should have a technical basis and resolve regulatory ambiguity.

GTTAC advised the Regulator as follows:

Resolution:

1. The committee supports a review of the Regulations.
2. Technical issues to consider:
    a. ability to detect the modification from some technologies may not be feasible, and

[2] *Identifying key developments, issues and questions relating to techniques of genome editing with engineered nucleases - Background paper* by Ainsley J. Newson & Anthony Wrigley for Nuffield Council on Bioethics

differentiating changes obtained through gene technology from random events may be difficult in some cases

b. similar technologies may produce modified organisms that differ in whether or not they are considered to be classified as GMOs
c. focus on risk as the starting consideration to determine the need for regulatory oversight