



15 December 2016

Regulations Review
Office of the Gene Technology Regulator (MDP 54)
GPO Box 9848, Canberra, ACT 2601

Re: Comments to the *Discussion Paper: Options for Regulating New Technologies* by the Office of Gene Technology Regulator, Australia

Dear Sir or Madam,

Dow AgroSciences LLC (DAS) is a leading developer of crop protection products and agriculturally important crop traits including increased yield, tolerances to diseases, insect pests and herbicides. By 2050, world food production must support an estimated 9 billion people. In order to meet the challenges of the growing world and ensure food security there is ongoing need for innovations in crop production technologies. DAS is committed to developing sustainable agricultural solutions that make farming more profitable and productive. DAS appreciates this opportunity to provide comments to the Office of Gene Technology Regulator (OGTR) on the *Discussion paper: Options for regulating new technologies* (Discussion Paper). Our comments pertain to the use of new breeding tools such as EXZACT™ Precision Technology¹ and similar genome editing techniques for use in creation of crop varieties and lines having improved traits. EXZACT™ is a site-directed, zinc finger nuclease (ZFN)-mediated genome modification technology which DAS has developed under an exclusive license and collaboration agreement in plants with Sangamo BioSciences, Inc. This technology is widely out-licensed globally for crop improvement.

DAS strongly supports Option-4 proposed in the Discussion Paper to exclude certain technologies based on the outcome they produce. This option proposes that if an organism carries genetic changes that are similar to or indistinguishable from the products of conventional breeding, they are to be excluded from being regulated as genetically modified organisms (GMOs). This would exclude organisms from regulation as GMOs when produced via oligonucleotide-directed mutagenesis (ODM), deletion of nucleotides by site-directed nucleases (SDN-1) or making one or few nucleotide changes using site-directed nucleases (SDN-2).

¹ DAS EXZACT™ website: <http://www.exactprecisiontechnology.com/what/>

Regulatory Rationale for Option 4:

A. Regulatory oversight based on properties of the products of biotechnology

Option-4 reaffirms the logic of focusing regulatory oversight on the properties of the products of biotechnology, rather than the processes by which they are developed. While we understand that a central policy setting of the Australian regulatory scheme involves a process trigger, this option continues the current policy of exclusions from regulation based on properties of the products. The range of crop improvement techniques that can be classified as “gene technology” is very broad and the use of any particular set of technique should not be subjected to any unique regulations or oversight. Instead, focusing on the products enables oversight to manage actual risks to health or the environment.

B. Regulatory oversight commensurate with risk to human health and the environment

As stated in the Discussion Paper, the intent of the Gene Technology (GT) Act is to protect human health and safety and to protect the environment. Existing GT Regulations exclude products of conventional breeding, including chemical or radiation mutagenesis, from the definition of GMOs as they do not pose any particular biosafety risk. As EXZACT™ Delete and EXZACT™ Edit (examples for SDN-1 and SDN-2, respectively) result in changes that are identical to changes that can occur through such conventional breeding techniques, products of these new techniques also pose no particular biosafety risk. Indeed, as explained above, because the intended changes are precise and fully characterized and the potential for unintended changes is minimal, products of EXZACT™ Delete and EXZACT™ Edit may pose less risk than those of conventional breeding techniques.

By contrast, EXZACT™ Add, as an example of SDN-3 techniques, results in the addition of new gene sequences and is analogous to, albeit more precise than, traditional transgenic technology (e.g. Agrobacterium-mediated or biolistic transformation). Products of EXZACT™ Add could theoretically pose biosafety risks associated with the inserted gene sequence and therefore regulation commensurate with such risks is appropriate.

C. Technical Background

Oligonucleotide-directed mutagenesis (ODMs) or Site-directed nucleases (SDNs) techniques such as EXZACT™ zinc finger nucleases (ZFNs) allow scientists to Delete (SDN-1), Edit (SDN-2) or Add (SDN-3) genomic DNA in plants. SDN-1 and SDN-2 can be used to precisely remove undesirable traits in plants –

such as anti-nutrients or allergens, in order to improve the nutritional value of a crop. It can also modify certain existing characteristics in a plant to respond to consumer needs such as enhanced shelf-life and improved taste or texture.

EXZACT™ Delete technique is used to delete undesirable DNA sequences to improve specific traits from the plant genome. EXZACT™ Edit allows scientists to re-write gene sequences to improve specific traits, while EXZACT™ Add allows a single gene sequence or a series of gene sequences (stack) to be added to a pre-determined genetic location within the plant genome.

Using EXZACT™ Delete, no repair template is needed. Once the targeted DNA sequence has been cleaved by EXZACT™ ZFNs, the cell will use another DNA-repair process known as Non-Homologous End-Joining (NHEJ) to resolve the double stranded break. This repair process sometimes results in short nucleotide deletions or insertions at the break site allowing the inactivation of genes and removal of undesirable plant traits.

In the case of EXZACT™ Edit a repair template is required. This repair template consists of the desired nucleotide modification to be made, in addition to homologous genomic sequence matching the sequences flanking the intended ZFN cleavage site. Once the ZFN cleaves the targeted DNA sequence, a natural plant DNA repair mechanism (homology directed repair, HDR) repairs the DNA break using the repair template and, in the process, encodes the modifications present on the template into the repair site.

With EXZACT™ Add, a repair template is also required, in this case bearing the desired new gene sequence(s) in addition to homologous genomic sequence matching the sequences flanking the intended ZFN cleavage site. In this case, HDR repairs the ZFN-induced DNA break using the template inserts the new gene sequence(s) into the repair site.

Several lines of evidence show that EXZACT™ ZFN designs are highly specific and can discriminate between intended and off-target sequences by as little as a single nucleotide of DNA sequence. For example, it has been shown in maize that EXZACT™ ZFNs targeting the maize IPK1 gene can differentiate between IPK1 and a highly similar (paralogous) gene IPK2 which differs by only a single nucleotide in the ZFP binding domains².

² Shukla *et. al.*, Nature 2009; vol. 459: p437-441

Genetic changes made using EXZACT™ Delete and Edit are indistinguishable, even at the molecular level, from mutations that can arise using chemical or radiation-induced mutagenesis or by traditional breeding methods. However, unlike alternative mutagenesis methods which result in the introduction of several random mutations in the plant genome, EXZACT™ mutations are pre-determined and targeted to a specific location, allowing scientists to significantly reduce the probability of unintentional and undesirable alterations at other genetic locations. By contrast, EXZACT™ Add results in products that are analogous to transgenic GMOs that are currently subject to regulation under the GT Act.

D. Transparent, predictable and efficient regulatory processes

Clarity and predictability help small/mid-size developers as well as larger developers such as DAS. Our company has to choose among competing projects when making investment decisions based in part on likelihood and timing of success. The greater the level of uncertainty, the fewer the projects can be prioritized. Regulatory delays have significant costs to developers in lost opportunity and return on investment. All other things being equal, developers of all sizes invest in projects that have the most predictable path and timing of regulatory success. While the descriptions of agency scope and oversight, provide indications as to the scope of the applicable regulations, it would be very helpful if the OGTR provided clear triggers for different levels of oversight that are based on risks associated with products. Option-4 provides predictability for developers when making investment decisions and strengthens international alignment.

The other options either do not resolve regulatory uncertainty (Option-1) or include under regulation products that do not present particular biosafety risks, as determined by the Gene Technology Technical Advisory Committee in its communique of its June 2016 meeting (Option-2 and Option-3). Over-regulation dramatically increases the costs of developing new products that improve the ability of agriculture to meet demands for food, fibre, and improved nutrition. Regulation of EXZACT™ Delete and EXZACT™ Edit would be counterproductive to the intent of the GT Act to be protective of human health and the environment.

E. International leadership

The OGTR Scientific Strategy 2013-2018³ provides an important emphasis on the organizations' leadership role. Because food production is global, international cooperation in regulatory systems is essential for successful deployment of innovations in agriculture. The Science Strategy calls for the OGTR to demonstrate to the national and international regulatory community how an evolving regulatory system that adapts to science based regulatory assessment will meet the shared goals of fostering innovation while protecting health and the environment. International partnerships promote public confidence in agricultural biotechnology products, increase transparency and predictability, and reduce unnecessary costs and burdens.

Conclusions

DAS is pleased that OGTR has initiated this public consultation of the Discussion Paper in reviewing options for regulation of new technologies and identified areas for improvement in predictability, communication and coordination. DAS strongly supports Option-4 which excludes certain techniques from regulatory oversight based on the outcomes they produce. It provides improved clarity of the existing regulatory systems on new techniques used to accelerate agricultural innovation while protecting human health and the environment.

We would be happy to discuss our comments further with OGTR.

Yours sincerely,

Dr. Matthew Cahill
R&D Leader,
Dow AgroSciences Australia Ltd

³ [http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/science-plan13-18-hm/\\$FILE/science-plan13-18-hm.pdf](http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/science-plan13-18-hm/$FILE/science-plan13-18-hm.pdf)