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

Re: Comments on proposed amendments to the Gene Technology Regulations 2001

The Agriculture Division of DowDuPont™, a business division of DowDuPont (NYSE: DWDP), combines the strengths of DuPont Pioneer, DuPont Crop Protection and Dow AgroSciences. Together, the Agriculture Division provides growers around the world with the most complete portfolio in the industry, developed through a robust research pipeline across germplasm, biotech traits and crop protection. The Agriculture Division of DowDuPont™ is committed to delivering innovation, helping growers increase productivity and ensuring food security for a growing global population. We appreciate the opportunity to provide comment on the *2016-17 Technical Review of the Gene Technology Regulations 2001.* Gene editing is one of the plant breeding tools that allows scientists to more precisely and efficiently improve a plant that could be obtained using traditional breeding methods or found in nature, helping farmers produce more and better food, with fewer resources. It is important that for these plant breeding innovations to be afforded the same regulatory regime as all similar plants, irrespective of the techniques used to develop them; if plants could be developed by a new plant improvement technique and by a conventional breeding technique, they should be regulated no differently.

Consultation Questions

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

The Agriculture Division of DowDuPont™ supports OGTR **Option 3** as per the Consultation Quick Guide and the Consultation Regulation Impact Statement (RIS), aiming to "*Amend the GT Regulations by introducing some, but not all, of the amendment elements from Option 2*". Adopting **Option 3** should result in clarifying that organisms produced by SDN-1 excluded from the GT (Gene Technology Act) regulation.

In the first round of consultation, the Agriculture Division of DowDuPont™ supported Option 4 as per the Discussion Paper: Options for Regulating New Technologies which proposed to exclude organisms produced by all three techniques (ODM, SDN-1 and SDN-2) from the GT regulation[1,2]. We continue to strongly believe that Option 4 most closely represents the current state of scientific knowledge and takes into account the baseline of safety established through the history of use of conventionally bred plant products and is supported by the intent, language, and structure of the Gene Technology Act 2000.

[1] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/8884A10B0BA5CF42CA2580B10016087D/$File/Dow%20Agrosciences%20Australia.pdf
[2] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/8884A10B0BA5CF42CA2580B10016087D/$File/DuPont%20Pioneer.pdf

Unfortunately, we understand that Option 4 has not been further taken up by OGTR as the OGTR considers it appropriate to regulate organisms developed using SDN-2 and ODM under the Gene Technology Act 2000. Two identified reasons for not excluding SDN-2 and ODM by the OGTR were:

- "*…excluding all organisms modified using SDN-2 and ODM from regulation may not be commensurate with risk, particularly with pests or disease-causing organisms."*

- *"Successive rounds of modification using SDN-2 or ODM could result in substantial changes which may pose risks warranting regulatory oversight*".

Thus, adopting the new **Option 3** as proposed by OGTR will result in a different regulatory regime of plant varieties produced with SDN-1 and varieties produced with oligo-directed mutagenesis or SDN-2 techniques. However, all three techniques (SDN-1, SDN-2 and ODM) can generate plants that do not contain "foreign" DNA (DNA from a different, sexually incompatible organism) and further, are indistinguishable from what could be produced using conventional breeding techniques or found in nature. Several examples illustrating this statement are provided in section 6 of this comment. Therefore, ODM and SDN-2 techniques are similarly not expected to produce organisms carrying any novel inherent risks as compared to those produced via traditional breeding or found in nature that would justify differential regulatory treatment. Further, as also acknowledged by OGTR that "*reliably detecting organism that might be indistinguishable from naturally occurring mutants or the products of techniques that are not gene technology presents a great challenge for enforcing compliance of the scheme*"[3] is again primarily related to the same technical underpinning, that products of SDN-1, SDN-2, and ODM techniques can be used to produce organisms that could likewise be produced using conventional breeding techniques or be found in nature.

Furthermore, the proposed regulatory regime of differentiating between plant varieties produced with SDN-1 and ODM/SDN-2 may discourage developers from using these latter techniques and impede commercialisation of the resulting products. SDN-2 and ODM may be limited to use for trait discovery and evaluation purposes only, whilst subsequently attempting to re-create the same product with traditional mutagenesis. This would be a superficial, time and resource consuming, and unguaranteed results approach that is incommensurate with the risk, yet resulting in the same end-product having different regulatory treatment based solely upon the process used.

We hope that as a part of the Department of Health's Review of the Gene Technology Scheme, the legislation will be amended to clarify and acknowledge the aforementioned scientific considerations to better promote and support the adoption of innovative breeding technologies within Australia to produce more and better food, with fewer resources.

[3] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/A0E750E72AC140C4CA2580B10011A68E/$File/Regulation%20Impact%20Statement%20for%20consultation.pdf, p.15

1. **Do the draft amendments clearly implement the measures describe 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?**

The Agriculture Division of DowDuPont™ supports in principle **Option 3** that is to introduce all elements of the draft amendments as per section 3 of the Consultation RIS. We do have concerns that in adopting Option 3, there will be a different regulatory regime of plant varieties produced with SDN-1 and varieties produced with oligo-directed mutagenesis or SDN-2 techniques despite all three techniques (SDN-1, SDN-2 and ODM) being able to generate plants that do not contain "foreign" DNA that are indistinguishable from what could be produced using conventional breeding techniques or found in nature. We have some suggestions to the language used in the proposed amendments that we believe will provide greater clarity, provided in the table below.

Topic Area	**Amended provision in the Gene Technology Regulations 2001**	**Amendment item in Gene Technology Amendment (2017 Measures No.1) Regulations 2017 (item in Schedule 1 unless noted otherwise)**	**Language Proposed by OGTR**	**Comment by Agriculture Division of DowDuPont™**
Clarifying scope of Regulation – What is a GMO				
Organisms modified using SDN-1 are not GMOs	Schedule 1 – new item	Item 32	Insert: 4 *An organism by repair of single-strand or double-strand breaks of genomic DNA induced by a site-directed nuclease, if a nucleic acid template was not added to guide homology-directed repair*	Amended Proposed Language: 4 *An organism <u>produced</u> by repair of single-strand or double-strand breaks of genomic DNA induced by a site-directed nuclease, if a nucleic acid template was not added to guide homology-directed repair, <u>and which does not contain DNA sequences from a vector used in the production process.</u>* We recommend focusing on the function or intent of this amendment, rather than specific tools, to ensure it is future-proofed for developments. For example, SDN-1 can be classified as a mutagenesis technique which would enable the inclusion of recombinases or other DNA modifying enzymes which have the same intended effect as a SDN-1 mutation. Furthermore, the use of the word *"modified"* could unintentionally imply the resulting product is somehow

				different from the same organism that is produced with traditional breeding techniques. Suggest change to *"an organism produced"*
Organisms modified using SDN-2 and ODM are GMOs	4A – new Schedule 1B – new	Item 31	Clause 31 *Insert: Schedule 1B – Organisms that are genetically modified organisms* *1 An organism that has had its genome modified by oligonucleotide-directed mutagenesis* *2 An organism modified by repair of single-strand or double-strand breaks of genomic DNA induced by a site-directed nuclease, if a nucleic acid template was added to guide homology-directed repair*	We do not support the inclusion of this language for the reasons previously identified in our comment and believe that inclusion of specific techniques is unnecessary given the current [Review of National Gene Technology Scheme]. Changes introduced using SDN-2 and ODM are comparable to the outcomes of techniques listed in Schedule 1A, Items 1, 2, 3, 4 and 10. From a human health and environmental risk perspective, the use of a template enables a specific and precise repair and an end product that could likewise result from traditional breeding or be found in nature. We believe that regulation should occur on the final product that is available in the public domain, not the process used.
Some RNAi techniques are not gene technology	Schedule 1A – new item	Item 30	Add: 11 Introduction of RNA into an organism, if *an organism, if:* *(a) the RNA cannot translated into a polypeptide; and* *(b) the introduction of the RNA cannot result in an alteration of the organism's genome sequence; and* *(c) the introduction of the RNA cannot give rise to an infectious agent*	Amended Proposed Language: 11 *<u>Exogenous application of RNAi to</u> an organism, if:* *(a) the RNA<u>i is</u> not translated into a polypeptide; and* *(b) the RNA<u>i does not</u> result in an <u>alteration</u> of the organism's genome sequence; and* *(c) the RNA<u>i does not</u> give rise to an infectious agent* The use of the word 'introduction' may cause a confusion as 'introduction' more commonly refers to the insertion of a gene into the genome.
Organism's derived from GMOs	Schedule 1 – two new items	Item 33	Add: Schedule 1 (at the end of the table) *8 An organism that is descended from a genetically modified organism (the initial organism), but which has not inherited any traits that occurred in the*	Amended Proposed Language: *8 An organism that is descended from a genetically modified organism (the initial organism), <u>but is absent of any genetic material modified by gene technology (a null segregant).</u>*

			initial organism because of gene technology. *9 An organism that was modified by gene technology but in which the modification, and any traits that occurred because of gene technology, are no longer present.*	*9 An organism that was modified by gene technology <u>but is absent of any genetic material modified by gene technology.</u>* In forward bred varietal crops such as soybean, genetic gain is a function of breeding effort. Genetic gain is experienced primarily in the GM breeding germplasm where more than most of the breeding effort resides. Deriving null segregant varieties from the most advanced breeding populations provides products to growers that choose to use conventional varieties which are comparable in performance to the most advanced GM varieties. Utilizing stringent quality control procedures, null segregant conventional varieties are identified, tested and advanced to commercial status[4]. We have proposed the language change to 8 to clearly identify the intent of including null segregants. We also propose minor language changes to 8 and 9 to provide clarity of intent and consistency. When considering the above statement on null segregants, we recommend language changes to both 8 and 9. In 8, rather than the phrase "but which has not inherited any traits that occurred in the initial organism because of gene technology" we suggest "but is absent of any genetic material modified by gene technology." Similarly in 9, we suggest replacing "but in which the modification and any traits that occurred because of gene technology, are no longer present." with "but is absent of any genetic material modified by gene technology."

[4] https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption/

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:

4.1 Clarifying the GT Regulations to take technological developments into account (i.e. in relation to SDN-1, SDN-2, ODM and RNAi)

The Agriculture Division of DowDuPont™ is the world leading expert in SDN-1 and SDN-2 gene editing for plants using CRISPR-Cas technology and has several product concepts in the R&D pipeline, including the most advanced SDN-1 based product, Next Generation Waxy Corn[5]. Innovative ideas are currently being sought for disease control, output, and yield & agronomics gene editing based traits in corn, soybean, rice, canola, sunflower and other oilseeds[6].
While SDN-1 and SDN-2 products are similar to those that could be achieved with conventional breeding tools, they can be developed much more efficiently and precisely. The technology allows to direct the genetic change and eliminate several breeding cycles, thereby shortening the product development timeline by several years[7]. The current GMO regulatory regime is associated with significant regulatory cost and lengthy regulatory approval process. If SDN-1 products are regulated in the same manner as compared to those produced via traditional breeding or found in nature, this would in turn regulate similar products in the same manner and potentially allow innovate products to be deployed more quickly as well as freeing-up resources to develop more products, including those focused on local solutions (e.g., resistance to regional diseases or specific consumer-oriented traits). In other words, the potential food safety risks of human and animal foods from SDN-2 gene edited plants are best addressed by considering the characteristics of the plants, just as with other existing plant development methods, rather than through the specific plant development method.
The Agriculture Division of DowDuPont™ is exploring a number of SDN-2 product concepts in several crops, for example development of corn hybrids with improved resistance to Northern Leaf Blight[8], a fungal disease impacting Australia as well[9]. The regulatory regime for SDN-2 crops as proposed by OGTR, associating these products with the current GMO regulatory requirements, would result in a need in prioritization and resource competition with large commodity GMO traits. The level of regulatory burden associated with a GM crop is not comparable nor befitting the process and product of a SDN-2 crop. As a result, SDN-2 product ideas that could benefit local growers or consumers.

4.2 Repeal of Schedule 1 item 1, specifically whether you currently work with organisms that are not GMOs solely because of this item

In forward bred varietal crops such as soybean, genetic gain is a function of breeding effort. Genetic gain is experienced primarily in the GM breeding germplasm where most of the breeding effort resides. Deriving null segregant varieties from the most advanced breeding populations provides products to growers that choose to use conventional varieties which are comparable in performance to the most advanced GM varieties. Utilizing stringent quality control procedures, null segregant conventional varieties are identified, tested and advanced to commercial status[4].

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[5] https://www.pioneer.com/home/site/about/news-media/news-releases/template.CONTENT/guid.1DB8FB71-1117-9A56-E0B6-3EA6F85AAE92
[6] https://www.pioneer.com/CMRoot/pioneer/about_global/our_research/pipeline/pipeline_2017.pdf
[7] https://seedinginnovation.org/wp-content/uploads/2016/10/CRISPR-Cas-infographic-2.pdf
[8] https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/17-076-01_air_inquiry_a1_cbidel.pdf
[9] http://www.pestnet.org/fact_sheets/maize_northern_leaf_blight_226.pdf

4.4 Clarifying the regulatory status of organisms derived from GMOs that are not themselves GMOs

Clarification of the regulatory status of organism derived from GMOs that are not themselves GMOs is essential for companies and research organisations who are working in this space, including Agriculture Division of DowDuPont™ because it provides guidance for making informed investment decisions. Due to regulatory certainty and acknowledgement of no need for an onerous regulatory regime, it will enable a more robust path to market for genotypically superior null sergeant breeding populations and SDN-1 varieties where transgenic material has been removed by segregation.

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.

As discussed in 4.1, Agriculture Division of DowDuPont™ believe that the products obtained and the potential risks to health and the environment from SDN-1 and SDN-2 are similar to those that can be achieved with conventional breeding tools. The long history of safe use of plant varieties produced through domestication and conventional breeding demonstrates that the specific techniques used to develop them do not pose an inherent safety risk. Gene editing techniques can result in plants found in nature or similarly be produced with conventional breeding, albeit in a much more targeted and efficient fashion. Thus, the same regulatory regime should be consistently applied to all similar products regardless of the technique used in their development; if plants could be developed by a new plant improvement technique and by a conventional breeding technique, they should be regulated no differently.

Specific examples of certain SDN-2 and ODM plant products that are non-distinguishable from plants that could be developed in a conventional breeding program or found in nature:

a) Various spontaneous and induced mutations in plant ALS (AHAS) genes leading to tolerance to sulfonylurea and imidazolinone herbicides have been described in several plant species[10,11] and commercialized in a range of crops[12]. Herbicide tolerance is conferred by specific amino acid changes in the ALS protein sequence. The same changes could be generated in maize and rice using CRISPR-Cas and TALEN mediated SDN-2 approach, and though oligo-directed mutagenesis approach in canola and predictably resulted in plant's herbicide tolerance[13,14,15.] Similar experiment was conducted in flax to generate two targeted amino acid changes in the native EPSPS gene resulting in glyphosate tolerance[16].

b) Targeted replacement (swap) of unfavourable NLB18 disease resistance allele in a maize variety of interest with the favourable NLB18 disease resistance allele of the same gene from another maize variety is another application of SDN-2 technique [8,17]. In this instance the homology directed repair involves a DNA template sequence that encodes the favourable

[10] Duggleby R.G. and Pang S.S. (2000) Journal of Biochemistry and Molecular Biology 33(1):
[11] Tan S. et al. (2005) Pest Management Science 61: 246.
[12] https://agriculture.basf.com/en/Crop-Protection/Clearfield-Global.html
[13] Svitashev S. et al. (2015) Plant Physiology 169: 931.
[14] Li T. et al. (2016) Journal of Genetics and Genomics 43: 207.
[15] http://www.cibus.com/technology.php
[16] Sauer N.J. et al. (2016) Plant Physiology 170: 1917.
[17] Custers R (2017) The regulatory status of gene-edited agricultural products in the EU and beyond. Emerging Topics in Life Sciences. DOI: 10.1042/ETLS20170019

allele. The favourable allele is brought into the recipient line at its native genomic location and replaces the current allele. Similar outcome can be achieved through a series of conventional breeding crosses although taking much longer time and potentially resulting in a genetic linkage drag due to a presence of the adjacent genetic material from the donor variety.

Agriculture Division of DowDuPont™ believes that the existing legislative framework does allow for the determination of SDN-2 and ODM as not GMOs. The 2001 Explanatory Statement to Schedule 1 of the Gene Technology Regulations 2001 (the "GT Regulation")[18] elaborates on two risk considerations based upon which organisms listed in Schedule 1 have been excluded from the GT Regulation. It identifies organisms resulting from certain technologies where the "process mimics natural mutation processes" and, accordingly, use of such technologies "give rise to organisms that can occur in nature, and as such do not pose a particular biosafety risk to the environment or human health and safety". Further, "Organisms that result from exchange of DNA within the same species (and where no genetic material from any other species is introduced) are not, therefore considered to be GMOs for the purposes of the regulatory scheme" due to the similarity to inherent cellular processes. Examples of oligo-directed mutagenesis, SDN-1, and SDN-2 developed organisms provided above illustrate that these organisms meet these criteria and thus pose a particular biosafety risk and should have the same regulatory treatment as organisms listed in Schedule 1 (i.e., considered to be not genetically modified).

Further, exclusion of SDN-2 and ODM from GMO regulation would be in alignment with Section 10 Definitions of the Gene Technology Act 2000, where:

*"**genetically modified organism** means:*
(a) an organism that has been modified by gene technology…"

whereas:

*"**gene technology** means any technique for the modification of genes or other genetic material, but does not include… (b) homologous recombination…"*

SDN-2 technique activates a plant's endogenous homology-directed repair (i.e., homologous recombination) mechanism to promote the target gene edit[19].

Item 1 of Schedule 1 (regulation 5), *"A mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)"* further aligns with the exclusion of SDN-2 and ODM from GMO regulation. Oligo-mediated mutagenesis, SDN-1, and SDN-2 are used to develop organisms that do not contain any foreign, non-homologous DNA sequences from another species. Absence of foreign DNA sequences (i.e., the SDN process components) can be confirmed through molecular assays if those components are delivered on plasmid vectors. RNA and protein based delivery methods, those not involving introduction of heritable genetic material, have also emerged and can be used to develop similar organisms[20,21,22] [10, 11, 12.]

[18] Explanatory Statement for the Gene Technology Regulations 2001 available at the Federal Register of Legislation (https://www.legislation.gov.au/Details/F2001B00162/Explanatory%20Statement/Text).
[19] Podevin N. et al. (2013) Trends in Biotechnology 31(6): 375.
[20] Woo J.W. et al. (2015) Nature Biotechnology 33(11): 1162.
[21] Zhang Y. et al. (2016) Nature Communications 7: 12617.
[22] Svitashev S. et al. (2016) Nature Communications 7: 13274.

Based on these comparable outcomes, we believe that SDN-2 is also excluded from the current regulatory regime. We advocate for further immediate review of this component of Option 3 once the current review of the *Gene Technology Act* 200 is complete.

In addition to the scientific rationale for inclusion of SDN-2 and ODM as not GMOs, it is important to consider the cost and burden to international trade (within Australia, regionally and globally) from Option 3. The potential implications of the implementation of Option 3 are disharmony from an import/export perspective and reticence of foreign countries to trade with Australia.

In the APAC region, the OGTR is a leading regulatory authority. Many smaller countries will look to the decisions of the OGTR and adopt. Given the asynchronous timeframes of the Department of Health review of the *Gene Technology Act* 2000 and the OGTR Technical Review of the Gene Technology Regulations 2001, the OGTR are unable to adopt Option 4 at present, however may do so in a further review of the regulations (post Act review). Other countries within the region may not have such flexibility to move forward with scientific developments and by adopting the concepts outlined in Option 3, may constrain their opportunities to trade in the international market. These trade related factors ought to be considered in alignment with the OGTR Scientific Strategy 2013-2018[23] which 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.

Agriculture Division of DowDuPont™ is pleased to participate in this public consultation with the OGTR and supports the commitment to a clear science-based regulatory policy providing improvements in predictability, communication and coordination. As a science company, the Agriculture Division of DowDuPont™ supports the adoption of the original Option 4, however we understand that this may not be considered possible under current legislation. We advocate and support regulatory reform in both the Act and the Regulations to allow the OGTR to operate under a regulatory regime that is based upon current scientific knowledge, is future-proofed for scientific developments, proportional to risk and promotes innovation. We thank the OGTR for this opportunity to comment and are happy to discuss further.

Yours sincerely,

Sarah Russell French
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[23] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/science-plan13-18-htm/$FILE/science-plan13-18-htm.pdf