Third Review of the National *Gene Technology Scheme*

Submission to the Department of Health and Ageing

15th September 2017

DuPont Pioneer

Gene Technology Review Secretariat
Department of Health and Ageing
MDP 138
GPO Box 9848
CANBERRA ACT 2609

RE: SUBMISSION TO THE AUSTRALIA GOVERNMENT'S, DEPARTMENT OF HEALTH & AGEING, 2017 REVIEW OF THE GENE TECHNOLOGY ACT 2000

Thank you for the opportunity to provide comment on the Australian Governments Gene Technology Act (2000) Review. DuPont Pioneer is a world leader in plant biotechnology and in Australia we are a seed genetics provider.

DuPont Pioneer is the world's leading developer and supplier of advanced plant genetics providing high-quality seeds to farmers in more than 90 countries. DuPont Pioneer provides agronomic support and services to help increase farmer productivity and profitability and strives to develop sustainable agricultural systems for people everywhere.

Pioneer Hi-Bred Australia Pty Ltd was founded in 1975. The company works closely with Australian farmers to develop seed products for the diverse agro-ecological environment in Australia. DuPont Pioneer has invested significantly in providing infrastructure that supports an Australia wide network of field staff and agronomists, each of whom provide in-field support to seed distributors and growers. We have an on-going commitment to expand this investment within Australia to service the supply chain involved in canola growing within the state.

In 2008 DuPont Pioneer was the first canola breeding company to release new varieties of GM canola into the Victorian and New South Wales canola markets. In 2009 Pioneer continued to be the market leader with the release of its GM canola varieties in Western Australia following the decision by the Western Australian Government to allow commercial cultivation of GM canola. In 2016 DuPont Pioneer obtained an authorisation from the OGTR (DIR 139) to commercially release its proprietary Optimum™ Gly herbicide tolerant canola in Australia.

In Australia, GenTech Seeds sells under license seed of proprietary Pioneer® brand corn, grain sorghum, forage sorghum as well as GM and non GM varieties of canola. DuPont Pioneer continues to undertake plant breeding and seed production in Australia. In addition, DuPont Pioneer has a number of research and development collaborations and investments with a number of Australia's leading private and public sector research institutions.

Yours sincerely

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DuPont Pioneer Response to the Terms of Reference (TOR)

TOR 1) Current developments and techniques, as well as extensions and advancements in gene technology to ensure the Scheme can accommodate continued technological development.

Plant breeding innovations, such as oligo-directed mutagenesis (ODM), SDN-1 and SDN-2 enabled gene editing, can contribute to addressing global challenges related to food security, population growth, sustainability, and climate change. However, practical application of these techniques in modern agriculture will inevitably be influenced by whether or not the regulatory regime treats their products in a manner commensurate with the potential risks they pose. DuPont Pioneer believes that any regulatory regime should be focused on the potential risks of a particular product regardless of the process used to develop it. It is the characteristics of the resulting plant, and not the method by which it was produced, that determines its safety.

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 result in plants that could be found in nature or 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.

DuPont Pioneer has previously submitted a comment[1] to the OGTR Review of the Regulations where it supports OGTR proposed Option 4, which most closely represents the current state of scientific knowledge and takes into consideration the baseline of safety established through the history of use of conventionally bred plant products. Option 4 enables the same regulatory treatment of plants produced with new technologies and those that can similarly be obtained with various conventional breeding tools – such as use of plant's own allelic variation, spontaneous mutations, or traditional induced mutagenesis. A few specific examples include:

- SDN-1 examples:
    - Targeted mutagenesis of FAD2 and FAD3 genes in soybean using TALENs[2,3] resulting in a high oleic phenotype. FAD2 and FAD3 mutants, both spontaneous and X-ray induced, have been described in soybean as well as other plant species[4].
    - Natural (spontaneous) or transposon induced mutations in maize MS fertility genes have been a subject of discovery and classical genetic studies for

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

[2] Haun W. et al. (2014) Plant Biotechnology J. 12: 934.

[3] Demorest Z.L. et al. (2016) BMC Plant Biology 16: 225.

[4] Pham A.-T. et al. (2010) BMC Plant Biology 10: 195.

decades[5]. One of such mutations, in MS45 gene, is a component of DuPont Pioneer's Seed Production Technology (SPT) process[6]. Most recently, targeted mutagenesis of MS genes in maize and several other monocots was achieved using CRISPR-Cas and meganuclease techniques[7,8].

- TALEN-mediated mutation of three *MLO* genes in hexaploid wheat resulting in resistance to powdery mildew[9]. The experiment was based on a prior knowledge about the loss-of-function *mlo* alleles existing in barley, Arabidopsis and tomato and shown to lead to resistance to fungal pathogens causing powdery mildew[10,11,12].

- SDN-2 and oligo-directed mutagenesis examples:

- 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[13, 14] and commercialized in a range of crops[15]. 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[16,17,18]. Similar experiment was conducted in flax to generate two targeted amino acid changes in the native *EPSPS* gene resulting in glyphosate tolerance[19].

    - Targeted replacement (swap) of unfavorable allele in a variety of interest with the favorable allele of the same gene from another variety is another potential application of SDN-2 technique. In this instance the homology directed repair involves a DNA template sequence that encodes the favorable allele. The favorable allele is brought into the recipient line at its native genomic location and replaces the current allele. Such an outcome is similarly achievable through conventional breeding by introducing the desired gene allele through a series of breeding crosses.

[5] Mutants of Maize, Neuffer M.G., Coe E.H., and Wessler S.R (eds) (1997) Cold Spring Harbor Laboratory Press: 311.
[6] Wu Y. et al. (2015) Plant Biotechnology J. 14: 1046.
[7] Svitashev S. et al. (2015) Plant Physiology 169: 931.
[8] Cigan A.M. et al. (2016) Plant Biotechnology doi: 10.1111/pbi.12633.
[9] Wang Y. et al. (2014) Nature Biotechnology 32(9): 947.
[10] Piffanelli P.et al. (2004) Nature 430: 887.
[11] Consonni C. et al. (2006) Nature Genetics 38: 716.
[12] Bai Y. et al. (2008) Molecular Plant Microbe Interaction 21: 30.
[13] Duggleby R.G. and Pang S.S. (2000) Journal of Biochemistry and Molecular Biology 33(1): 1.
[14] Tan S. et al. (2005) Pest Management Science 61: 246.
[15] https://agriculture.basf.com/en/Crop-Protection/Clearfield-Global.html
[16] Svitashev S. et al. (2015) Plant Physiology 169: 931.
[17] Li T. et al. (2016) Journal of Genetics and Genomics 43: 207.
[18] http://www.cibus.com/technology.php
[19] Sauer N.J. et al. (2016) Plant Physiology 170: 1917.

The 2001 Explanatory Statement to Schedule 1 of the Gene Technology Regulations 2001 (the "GT Regulation")[20] 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 do not 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 from GMO regulation under Option 4 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[21].

Option 4 will be also in alignment with the current **Item 1 of Schedule 1 (regulation 5)** that describes *"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)"* as organisms that are not genetically modified. 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[22,23,24].

[20] 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).
[21] Podevin N. et al. (2013) Trends in Biotechnology 31(6): 375.
[22] Woo J.W. et al. (2015) Nature Biotechnology 33(11): 1162.
[23] Zhang Y. et al. (2016) Nature Communications 7: 12617.
[24] Svitashev S. et al. (2016) Nature Communications 7: 13274.

Thus, DuPont Pioneer supports Option 4 as being based on current scientific knowledge and in alignment with the risk criteria explained in the GT Regulations that certain organisms are not GMOs and do not pose any unique biosafety risks to the environment or human health and safety due the processes used in their development. Accordingly, consistent with OGTR's current policies, DuPont Pioneer proposes that OGTR updates Schedule 1A of Section 5 and/or Item 1 of Schedule 1 to clarify that organisms obtained with a use of oligo-directed mutagenesis and SDN-1 and SDN-2 targeted mutagenesis that do not contain any foreign, non-homologous DNA sequences from another species are similarly not GMOs and do not present a unique biosafety risk.

DuPont Pioneer further supports the AusBiotech, The Australian Academy of Technology and Engineering (ATSE) and the Australian Academy of Science (AAS) recommendation that the OGTR adopts an exemption model for those techniques that result in products indistinguishable from those that could be made using conventional breeding, spontaneous mutations or classical (chemical, irradiation) mutagenic techniques, considering that:

a) Extensive genetic variations have been introduced into plants and animals by a range of previously available breeding techniques that have historically been accepted without a need for GMO regulation.

b) Plants and animals modified using new technologies should not be differentially regulated if they are similar to, or indistinguishable from, those that could have been produced through earlier breeding methods (i.e. those exempted from regulation under Schedule 1A).

TOR 2) existing and potential mechanisms to facilitate an agile and effective Scheme, which will ensure continued protection of health and safety of people and the environment.

Continuing challenges face the Australian agriculture and food sector; namely, the declining terms of trade, protectionist international trading policies and in some areas significant land and water degradation. New challenges are emerging that will also have impacts on Australian agriculture. Some issues of importance include:

- The increasing importance of consumer demand for markets
- Maintaining the competitiveness of Australian products in the international marketplace
- Increasing importance of efficient and well-linked supply chains
- Appropriate infrastructure, for example transport, communication, water and energy availability
- Higher demands on management skills and access to suitable skilled labour
- Sustainable resource management
- Encouragement of research and development in the agriculture and food sectors
- Impacts of climate variability and change

Amongst the plethora of technologies that will be developed and applied to resolving these issues, the pre-eminent technological development will come from plant sciences. Plant sciences utilize diverse technologies with outputs far broader that just GM crops. Various techniques can be used to facilitate variety development and screening strategies in conventional breeding programs, to identify and source new variations in land races and wild relatives and to better understand the genes controlling plant responses. The use of molecular markers to track genes or groups of genes responsible for complex traits increases the breeding precision and greatly reduces the time required for conventional breeding programs. Gene editing is a plant breeding innovation which is based upon a knowledge of plant's gene function, utilizes genetic sequences from the same plant/crop, and results in a targeted change of a plant's own gene without introducing any DNA sequences from non-sexually compatible species into a resulting organism.

It is critical to the future use of these technologies in Australian agriculture that gene technology regulation in Australia remains consistent with its current aims, but at the same time enables the flexibility to reflect developments in the field of plant science technologies, including the use of plant breeding innovations.

The most effective way for the delivery of an agile and effective Scheme, which will ensure continued protection of health and safety of people and the environment is for the OGTR to focus on the implementation of a nationally consistent system that is science-based, rigorous and transparent. The process should also promote innovation and provide a clear and predictable path-to market.

To facilitate the delivery of an agile and effective Scheme, now and into the future, DuPont Pioneer would recommend that the following be adopted as part of the current review of the Act:

1) The Act currently captures a wide range of related technologies, including processes that result in plants that could be obtained using conventional breeding technique or that mimic processes occurring in nature. With the advent of such new technologies (refer response to TOR 1), definitions relating to GMOs (e.g., gene technology and genetically modified organism) captured within the Act should be reviewed and at the same time harmonised with agencies such as Food Standards Australia and New Zealand (FSANZ) and the Australian Pesticides and Veterinary Medicines Authority (APVMA).

2) Since the inception of the Scheme there have been a number of advancements which are available to the OGTR in their assessment of an application for an intentional release authorisation. These include:

    a. the use by the OGTR of species specific biology documents which have been prepared to inform the Regulator's Risk assessment and Risk Management Plans in response to licence applications for clinical trials, field trials or release of genetically modified organisms into the environment. For plant species such as canola, cotton and safflower these documents detail current knowledge relating to a broad range of topics covered within an application (e.g., pollen flow, weedy relatives, etc.), and

    b. the generation of extensive published research relating to various enabling technologies (e.g. RNAi)

    DuPont Pioneer recommends that based on these advancements the OGTR adopt a tiered structure for approval where the time frame for approval of the application is determined by an initial assessment of the level of data required to be generated by the applicant for inclusion in the application. The level of data being determined by a pre-assessment data gap analysis undertaken by the application in consultation with the OGTR or its Institutional Biosafety Committee (IBC).

    For example, where an application is for a plant species where an OGTR species biology document can be referenced (e.g., canola) and the proposed trait (e.g., oil profile modification) is based on a well characterised technology (e.g., RNAi), then the time allocated for assessment and approval should be significantly less than an application where this supporting information does not exist and requires generation.

    These advancements should be reflected in the ability of the Gene Technology Regulator (GTR) to provide approvals where the opportunity exists earlier than the statutory time frame (255 days) that exists within the Scheme. This would be of

significant benefit to researchers and the broader industry for development and commercialisation of innovative products derived from biotechnology.

3) To further facilitate delivery of an agile and effective Scheme, which will ensure continued protection of health and safety of people and the environment DuPont Pioneer recommends that the OGTR adopts a more flexible and responsive framework within which it operates. This framework should recognise the pace of change in the sector by proactively allowing the GTR through consultation and, if required, through regulation, the ability to address changes in gene technology in a timely and efficient manner than what the current framework allows.

   DuPont Pioneer supports changes to the time frames for modifications to the Act and/or the Regulations (i.e. reduced to 3 years), both of which currently require significant and un-acceptable lead and implementation time frames.

   AusBiotech supports the proposed approach of AusBiotech, The Australian Academy of Technology and Engineering (ATSE) and the Australian Academy of Science (AAS) in their proposal to increase the powers and responsibilities of advisory bodies to the GTR, for example, Gene Technology Technical Advisory Committee (GTTAC) could have a more defined role in advising and making recommendations to the GTR on advancements in gene technology and associated enabling technologies within the context of the current and future legislative and regulatory framework (i.e. do they require regulation or not and if so, do they fall within the current framework or are changes required in regulation and/or legislation).

TOR 3) the appropriate legislative arrangements to meet the needs of the Scheme, now and into the future, including the Gene Technology Agreement.

1) The Federal Act and the Gene Technology Agreement.

The object of the Act is to "protect the health and safety of Australians and the Australian environment from risks posed by, or as a result of, gene technology by identifying those risks and managing them by regulating certain dealings with genetically modified organisms (GMOs)".

Within the definition of the current Act, the OGTR is achieving the Acts objectives via the framework it has adopted for the assessment of risk which is based on a rigorous science-based approach.

Where the "spirit" of the Act has not been achieved is where State and Territory government legislations relating to "Market Choice" (i.e. economics, markets and trade) have been allowed (directly or indirectly) to influence the ability to commercialize biotech crops (e.g., GM canola) that have been approved by the OGTR as being safe to human and animal health and the environment. DuPont Pioneer believes that the only acceptable role of the Federal, State and Territory governments for becoming engaged in market related matters is where there has been clear market failure.

In the case of GM canola, the grains industry supply chain addressed concerns raised by State and Territory governments in relation to market issues by issuing a statement entitled "Delivering Market Choice with GM canola"[25].

The industry agreed that it could deliver the three key elements of market choice:

- the ability of any supply chain participant to source product that meets a predetermined set of specifications
- the ability of any supply chain participant to supply product that meets a predetermined set of specifications
- the ability of any supply chain participant to manage their area of the production, processing, manufacturing and delivery of product to a pre-determined set of specifications.

Despite this commitment from the grains industry in addressing the issue's raised, various State and Territory governments proceeded to impose moratorium under their respective legislation. The lack of consistency in dealing with GM canola between the Federal and State/Territory governments was further emphasized by the lack of consistency and continuity between the States and Territories in nominating criteria and processes for the approval for growing of GM canola commercially.

[25] http://www.afaa.com.au/pdf/Delivering_Market_Choice_with_GM_canola.pdf

Providing a product is proven to be safe under The Act and its origins can be independently traced to support that claim, then it is the role of the market within a free trade economy to determine if the benefits the product offers to consumers and/or the supply chain are acceptable or not, when compared to current alternative options. The market remains free to choose the product or not. If the product provides these benefits then it will be adopted, if not - then the product will not remain in the market.

DuPont Pioneer strongly encourages the Federal government to initiate a proactive engagement process with its counter parts in State and Territory governments via the Legislative and Governance Forum on Gene Technology to re-establish continuity and consistency in the application of the principles expressed in the Act and reflected in the Inter-Government Gene Technology Agreement.

2) Monitoring and Compliance

The OGTR has to be commended on its approach to the manner in which it monitors and enforces compliance within the powers of The Act. From being a key point of conflict between the regulator and stakeholders, the manner in which OGTR currently engages with stakeholders has evolved to a position where this is no longer seen as point of contention.

Rather, the compliance process between the OGTR and stakeholders is now a proactive process in which a collaborative prevention approach has been adopted rather than the original enforcement- punitive approach.

However, due to the introduction of various State and Territory legislations relating to the growing and management of GM crops and pastures, a significant level of inconsistency now exists between the Federal and State/Territory based approaches to compliance.

This inconsistency in relation to compliance at a State and Territory level has resulted in the imposition of unrealistic restrictions (e.g., banning the transport of GM canola seed in South Australia), compliance practices and management costs, even when the GM crop has been approved as being safe to human and animal health and the environment by the OGTR.

Due to the lack of consistency between the OGTR and its governance of compliance and the approach taken by respective State and Territory governments, there is a lack of confidence in a predictable and clear path to market for new approved products. If this inconsistency is allowed to persist it will continue to be detrimental to introducing innovative agricultural products to Australia.

DuPont Pioneer strongly encourages the Federal government to initiate a proactive engagement process with its counter parts in State and Territory governments via the Legislative and Governance Forum on Gene Technology to re-establish continuity and consistency in the application of the principles expressed in the Act and reflected in the Inter-Government Gene Technology Agreement.

TOR 4) funding arrangements to ensure sustainable funding levels and mechanisms are aligned with the level and depth of activity to support the Scheme.

The obligation of the regulatory system is to serve both the public and private sectors of research and development, as such the basic dilemma for the OGTR is to establish a cost structure which is equitable to all participants and that does not differentiate between each sector.

Currently, the administrative compliance cost structure, implemented by the OGTR for regulatory requirements for classes of approval under the Act is commensurate with the level of risk and the expectations of stakeholders.

However, in relation to the imposition of administrative costs relating to compliance there is a distinct gap between what is realistic and equitable as administered by the OGTR versus State and Territory compliance systems which have fundamental flaws on which it is undertaken. Hence, for there to be equity between the Federal and State/Territory compliance cost structure, there needs to be a fundamental realignment of the operating principles of the OGTR and that of State and Territory governments, in relation to compliance. Where appropriate, alternatives to compliance based legislation should be employed, particularly in the areas of evaluating market and economic factors, which should be determined by the industry / market place.

In closing, DuPont Pioneer appreciates OGTR's commitment to a clear regulatory policy which will enable the Australian plant industry to operate in a predictable and science-based regulatory environment. As a science company, DuPont Pioneer supports a regulatory regime which is based on current scientific knowledge, proportional to risk, and promotes innovation. Scientifically unjustified and unnecessarily onerous regulatory requirements will stifle innovation, preventing beneficial products from entering the market, and likely narrow application of new technologies to a handful of high margin commodity crops while significantly limiting their potential adoption by small and medium organizations across wide range of crops.

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