



**Australian Government**

**Department of Health and Ageing**

**Office of the Gene Technology Regulator**

## **Review of the Gene Technology Regulations 2001**

### **Discussion Paper No. 2 (2010)**

#### **Review of the classification of Notifiable Low Risk Dealings**

### ***Introduction***

A number of proposed amendments to the Gene Technology Regulations 2001 (the Regulations) relate to scheduling of dealings with GMOs as notifiable low risk dealings (NLRDs). The *Gene Technology Act 2000* (the Act) creates the category of NLRDs, providing for the Regulations to declare a dealing with a GMO to be an NLRD.

The requirements for declaring particular dealings to be NLRDs are set out in Sections 74 and 75 of the Act, and include that the Gene Technology Regulator (the Regulator) must:

- be satisfied that the dealing would not involve the intentional release of a GMO into the environment; and
- consider :
  - whether the GMO is biologically contained so that it is not able to survive or reproduce without human intervention; and
  - whether the dealing would involve minimal risk to the health and safety of people and the environment; and
  - whether any conditions are necessary to manage any risks associated with the properties of the GMO.

Further detail on the requirements of the Act is provided at Appendix 1 (*Legislative background to NLRDs*).

Dealings with GMOs that are classified as NLRDs are defined by Regulation 12, supported by Schedule 3 of the Regulations. Integral to the definition of NLRDs in Regulation 12 is that these dealings do not involve an intentional release of the GMO into the environment. Parts 1 and 2 of Schedule 3 describe kinds of NLRDs which generally must be conducted in facilities certified by the Regulator to at least physical containment (PC) level 1 and level 2, respectively (see *Containment of NLRDs* below). Importantly, Part 3 (dealings which are not notifiable low risk dealings) qualifies the lists in Parts 1 and 2, so that a dealing of a kind described in Part 3 is not an NLRD even if it meets a description in Part 1 or Part 2. Dealings which do not meet the requirements for classification as exempt dealings or NLRDs must only be conducted if authorised by a licence issued by the Regulator.

## ***Proposed changes***

### **Proposal 1 – GM laboratory strains of rabbits and guinea pigs as PC1 NLRDs**

It is proposed that dealings involving genetically modified rabbits and genetically modified guinea pigs be classified as NLRDs suitable for containment in PC1 facilities, with the same conditions as currently required for dealings with GM mice and rats.

Currently, dealings with GM laboratory strains of mice and rats are listed in Part 1 of Schedule 3 of the Regulations (NLRDs suitable for containment in PC1 facilities), provided the genetic modification does not confer an advantage on the animal or lead to the production of infectious agents. Dealings with GM laboratory mice and rats where the genetic modification confers an advantage are classified as PC2 NLRDs, and dealings with those producing infectious agents require a licence.

Consideration was given to including dealings with GM laboratory strains of rabbits and guinea pigs in this classification. The risks posed by dealings with GM rabbits and guinea pigs were assessed in the context of NLRD requirements and the dealings being conducted in PC1 facilities. PC1 animal facility requirements include keeping animals in containers or cages when not being handled. The facility must also be designed to prevent escape of the animals being contained, and any openings (such as windows, vents and drains) must be screened. It was concluded that escape of a rabbit or guinea pig from a PC1 facility is highly unlikely, even during handling of the animals.

Both rabbits and guinea pigs are exotic to Australia. European (Spanish) rabbits were introduced to Australia in the 1800s and have established as a major feral pest. However, domesticated breeds of rabbits do not compete well with feral rabbits and are not able to survive as effectively in the environment as feral rabbits. Guinea pigs were introduced into Australia at least 30 years ago and there is no evidence to date of the establishment of feral populations. Because of the poor competitive ability of laboratory strains of rabbits and guinea pigs, dealings with these animals in containment are considered to pose minimal risk to the environment.

Domestic rabbits and guinea pigs are not considered to pose a significant risk to human health and safety. There is a history of safe domestic and research use of rabbits and guinea pigs in Australia.

The conclusion of the risk assessment is that PC1 containment and other NLRD requirements would adequately manage any risks to human health and safety and the environment posed by dealings with GM laboratory strains of rabbits and guinea pigs. A key consideration in reaching this conclusion is the prescribed containment requirements that would apply. On this basis, it is proposed that dealings with GM laboratory rabbits and guinea pigs be scheduled as PC1 NLRDs, similarly to dealings with GM rats and mice. As is currently the case for dealings with GM laboratory strains of mice and rats, it is proposed that PC1 NLRD classification of dealings with GM laboratory strains of rabbits and guinea pigs be conditional on the genetic modification not conferring any advantage or any ability to secrete or produce infectious agents.

## **Proposal 2 – GM plants**

It is proposed that the scheduling of containment requirements for GM plant NLRDs be simplified, to remove redundancy with respect to reproductive material.

This proposal would be accomplished by modifying Schedule 3 Part 2 by deleting paragraph (ba) and amending paragraph (b) to read:

*(b) a dealing involving a genetically modified plant.*

Most dealings with GM plants in containment are classified as NLRDs. The current clauses in Schedule 3 Part 2 which capture GM plants are as follows:

- (b) a dealing involving a genetically modified plant (including a genetically modified flowering plant), if the dealing occurs in a facility that is designed to prevent the escape from the facility of:
  - (i) pollen, seed, spores or other propagules which may be produced in the course of the dealing; and*
  - (ii) invertebrates that are capable of carrying the material mentioned in subparagraph (i);**
- (ba) a dealing involving a genetically modified flowering plant, if, before flowering, all inflorescences are wholly enclosed in bags designed to prevent escape of viable pollen and seed;*

From the time the Regulations were made in 2001, the classification of dealings with GM plants as NLRDs has been subject to the requirement that propagative material from the GM plants be contained. Unlike other NLRD clauses, these clauses include some specification of the details of containment measures, such as using a facility designed to prevent escape of pollen or bagging of inflorescences. Noting that subregulation 13 (2) already requires use of a facility *appropriate* for the kind of NLRD being undertaken, it is proposed to simplify these two clauses to remove details of containment requirements, and to provide these requirements through the guidelines and certification instruments for PC2 plant facilities.

It should be noted that the scheduling of dealings with GM plants would not change as a result of this proposal.

## **Volume of GMO culture**

### **Proposal 3.1 – Dealings which become NLRDs over a specified volume**

It is proposed to amend Schedule 3 Part 2 to increase the volume of culture of exempt host/vector systems above which a dealing is classified as an NLRD, from 10 to 25 litres.

### **Proposal 3.2 – Dealings which are NLRDs below a specified volume**

It is proposed to amend Schedule 3 Part 3 to increase the volume of culture of GMOs other than exempt host/vector systems above which dealings require licensing, from 10 to 25 litres.

These proposals correspond with a proposal described in a separate paper, that the maximum volume of culture of exempt host/vector systems which can be dealt with as an exempt dealing be increased from 10 to 25 litres per vessel (see *Review of the Classification of Exempt*

*Dealings*, proposal 3). As is discussed in that paper, an assessment of risk and its management, based on regulatory experience gained since the commencement of the Act, indicates that dealings involving cultures of up to 25 litres per vessel are suitable for categorisation as exempt. In making this proposal, a primary consideration is the suitability of facilities to contain and manage large culture spills. OGTR's experience is that dealings with cultures of greater than 25 litres are appropriate only for facilities designed for such large scale work and where the certification requirements include measures to manage large culture spills. For other facilities dealing with smaller culture volumes, such measures are considered unnecessary.

Schedule 2 of the Regulations currently restricts exempt dealings with GMO cultures to volumes of no more than 10 litres per vessel. Above this volume, Schedule 3 Part 2 paragraph (f) requires that dealings which would otherwise be exempt are classified as NLRDs suitable for PC2 large scale facilities.

Schedule 3 Part 3 paragraph (k) classifies as a licensable dealing (eg a Dealing Not involving Intentional Release) any dealing involving more than 10 litres of GMO culture, other than a dealing described at Part 2 paragraph (f) (ie other than GMO cultures of listed exempt host/vector systems involving donor nucleic acid considered low risk).

It is proposed to amend the volume specified in Schedule 3 Part 2 (f) and Schedule 3 Part 3 (k) from 10 to 25 litres, consistent with OGTR's operational experience. Under the proposed changes, the classification of dealings involving cultures of greater than 25 litres would remain unchanged (ie NLRD or a licence, depending on the specific case). The classification level of dealings involving cultures of between 10 and 25 litres would decrease from NLRD to exempt for dealings with listed exempt host/vector systems carrying low risk donor nucleic acid, and from DNIR to NLRD for other dealings.

#### **Proposal 4 – Introduction of a GMO into a human (somatic cell gene therapy)**

It is proposed to amend Schedule 3 Part 3 (m) of the Regulations to no longer require licensing of dealings involving introduction into a patient of genetically modified human somatic cells which are incapable of secreting any infectious agents. This proposal would support Section 10 of the Act and improve consistency between the Act and the Regulations.

The definition of a GMO in the Act specifically excludes people who have undergone somatic cell gene therapy from being considered GMOs in the regulatory scheme, so once the cells are introduced, the patient (including any GM somatic cells) is not subject to regulation under the Act.

Currently, the introduction of a GMO into a human, including GM somatic cells for the purpose of gene therapy, is classified as a licensable dealing. This requirement was introduced with the Gene Technology Amendment Regulations 2006, through the listing in Schedule 3 Part 3, at paragraph (m), of “a dealing involving the intentional introduction of a GMO into a human being”. It was considered that authorisation of such dealings warranted individual assessment by the Regulator of potential risks to human health and safety and the environment. The Regulator's assessment in respect of human health focuses on a consideration of risks to humans other than recipient patients.

More recent consideration has identified specific circumstances where undertaking somatic cell gene therapy poses negligible risk to human health and safety from the GMO, which are:

- when human somatic cells are isolated from a patient (or a compatible donor), genetically modified and reintroduced into the patient; and
- when the modified cells are not capable of secreting infectious agents.

It should be noted that clinical trials involving somatic cell gene therapy are overseen by Human Research Ethics Committees and/or the Therapeutic Goods Administration, who must consider patient safety and efficacy. Further information about the oversight of human clinical trials is provided in appendix 1 (see *Oversight of human clinical trials*).

It is proposed that the Regulations be amended to clarify that the introduction of human GM somatic cells that are incapable of secreting any infectious agents into a human being does not require a licence. Dealings with the GM human cells prior to introduction into the patient would continue to be regulated according to their classification in Schedules 2 and 3 of the Regulations.

### **Proposal 5 – Classification of dealings with Risk Group 3 and 4 microorganisms as DNIRs**

It is proposed that dealings with GM Risk Group 3 and Risk Group 4 microorganisms be excluded from classification as NLRDs, with the result that such dealings would require licensing. This proposal addresses a potential inconsistency between the level of containment of such dealings required by the Regulations, and recognised laboratory best practice.

*AS/NZS 2243.3 Safety in laboratories – microbiological aspects and containment facilities* (the Standard) is a standard published jointly by Standards Australia and Standards New Zealand. Although it is not legally binding, the Standard is widely recognised as best practice for safety in microbiological laboratories, and is adhered to by the majority of Australian research institutions, clinical facilities and pathology laboratories. Physical containment requirements described in the Standard form the basis of the Regulator’s certification guidelines for facilities.

The Standard classifies microorganisms into four risk groups (RG1-4) on the basis of the risks they pose to individuals (eg their potential to cause serious disease) and to the community (eg whether preventive measures or treatments are available). Risk Group 3 and 4 microorganisms are defined in the Standard as follows:

*Risk Group 3 (high individual risk, limited community risk)—a pathogen that usually causes serious human or animal disease and may present a serious hazard to laboratory workers. It could present a risk if spread in the community or the environment, but there are usually effective preventive measures or treatment available. Examples: Bacillus anthracis, Brucella, HIV, Yellow fever, tick-borne viruses.*

*Risk Group 4 (high individual and community risk)—a pathogen that usually produces life-threatening human or animal disease, represents a serious hazard to laboratory workers and is readily transmissible from one individual to another. Effective treatment and preventive measures are not usually available. Examples: Ebola virus, Hendra virus, tick-borne encephalitis.*

The Standard indicates that work with RG3 and RG4 microorganisms should be carried out in PC3 and PC4 facilities, respectively, to manage risks to human health and safety.

Current classification of dealings as NLRDs in the Regulations gives consideration to the capacity of the genetic modification to change the ability of the host or vector to cause harm, but not to the inherent risk posed by the unmodified host or vector. An unintended

consequence of the current scheduling clauses is that dealings with GM RG3 and RG4 microorganisms might be classified as PC2 NLRDs, provided the GMO poses no increased risk compared to the parent organism.

The Regulations prescribe the level of containment required for NLRDs, with PC2 being the highest containment level that can be prescribed. Regulation 13 (2) (a) (ii) indicates that PC2 NLRDs (Schedule 3 Part 2) must be conducted in facilities certified to at least PC2 and of appropriate design for the dealing. OGTR advises organisations that containment of GM RG3 microorganisms should be in accordance with the standard, and operational experience indicates that any such dealings are being conducted in appropriate containment. Certification guidelines for PC2 laboratories (and higher level containment facilities) also include specific requirements in relation to containment, including biological safety cabinets.

Section 74 (3) indicates that consideration of whether particular dealings with GMOs may be classified as NLRDs includes whether they involve minimal risks to human health and safety and the environment, taking account of the properties of the GMO as a pathogen and whether no or minimal conditions need be prescribed to manage those risks.

As a result of these considerations, it is proposed that dealings with GM RG3 and RG4 microorganisms be excluded from classification as NLRDs. The requirement that such dealings be licensed would ensure that appropriate containment requirements can be imposed upon such dealings. The proposed change is in line with the requirements of Section 74 of the Act, and would provide clarity for researchers and Institutional Biosafety Committees (IBCs) about the containment requirements appropriate for dealings involving GM RG3 and RG4 microorganisms.

This change would require organisations wishing to continue dealings with RG3 and RG4 microorganisms, currently authorised pursuant to notification as NLRDs, to apply to the Regulator for a DNIR licence. However, the amendments also provide for a transition period of one year to allow researchers to apply for a DNIR licence.

It should also be noted that the Standard is currently under review, and publication of an updated version is expected in 2010. If possible, references to the Standard will be updated prior to finalising the Gene Technology Amendment Regulations 2010.

## **Appendix 1 Legislative background to NLRDs**

### **NLRD classification**

The Act requires the Gene Technology Regulator (the Regulator) to consider certain matters before a dealing is declared to be an NLRD. These matters are described in Section 74 (2) and (3) of the Act:

- (2) *Before the Governor-General makes regulations declaring a dealing with a GMO to be a notifiable low risk dealing, the Regulator must be satisfied that the dealing would not involve the intentional release of a GMO into the environment.*
- (3) *Before the Governor-General makes regulations declaring a dealing with a GMO to be a notifiable low risk dealing, the Regulator must consider the following matters:*
  - (a) *whether the GMO is biologically contained so that it is not able to survive or reproduce without human intervention;*
  - (b) *whether the dealing with the GMO would involve minimal risk to the health and safety of people and to the environment, taking into account the properties of the GMO as a pathogen or pest and the toxicity of any proteins produced by the GMO;*
  - (c) *whether no conditions, or minimal conditions, would be necessary to be prescribed to manage any risk referred to in paragraph (b).*

Regulation 12, supported by Schedule 3 of the Regulations, defines what dealings with GMOs are classified as NLRDs. Dealings included in the NLRD classification in the Regulations, as they were originally made in 2001, were based upon Genetic Manipulation Advisory Committee (the body who had oversight of the former voluntary scheme for the regulation of gene technology) Category B activities. Such activities had been assessed over time as presenting minimal biosafety risks.

Before a person can commence an NLRD, subregulation 13(1) requires that an IBC assess the proposed dealing to be an NLRD (according to the descriptions in Schedule 3). This ensures that dealings being conducted as NLRDs are correctly classified. NLRDs which have been assessed by IBCs must be notified to the Regulator by the responsible organisations in their annual report (regulation 13A).

### **Containment of NLRDs**

Section 75 (2) of the Act provides for the Regulations to specify the conditions which will apply to NLRDs:

- (2) *The regulations may prescribe different requirements to be complied with in different situations or by different persons, including requirements in relation to the following:*
  - (a) *the class of persons who may undertake notifiable low risk dealings;*
  - (b) *notifying the Regulator of notifiable low risk dealings;*
  - (c) *supervision by Institutional Biosafety Committees of notifiable low risk dealings;*
  - (d) *the containment level of facilities in which notifiable low risk dealings may be undertaken.*

Regulation 13 establishes the conditions and requirements that must be complied with by a person proposing to undertake, or who is undertaking, an NLRD. Subregulation 13(2) prescribes the containment requirements for NLRDs:

- (2) *A notifiable low risk dealing must comply with the following requirements:*
- (a) *the dealing must be conducted:*
    - (i) *for a kind of dealing mentioned in Part 1 of Schedule 3 — in a facility that is certified by the Regulator to at least physical containment level 1 and is of appropriate design for the kind of dealing being undertaken; or*
    - (ii) *for a kind of dealing mentioned in Part 2 of Schedule 3 — in a facility that is certified by the Regulator to at least physical containment level 2 and is of appropriate design for the kind of dealing being undertaken; or*
    - (iii) *in another facility in accordance with any technical and procedural guidelines relating to containment of GMOs, as in force from time to time under paragraph 27 (d) of the Act, that the Regulator has determined in writing are appropriate for conducting the dealing;*

Thus NLRDs may be conducted either: in a facility certified by the Regulator to the indicated containment level (or a higher level); or, where the Regulator has determined in a specific case that another type of facility is appropriate, in a facility meeting applicable guidelines.

The requirement in the Regulations for use of a facility “*of appropriate design*” for the kind of dealing means that not every facility certified at a particular PC level may be used for any dealing requiring that level. For example, a PC2 laboratory will generally not be appropriate for dealings involving GM animals, and a PC2 animal house will generally not be appropriate for dealings involving GM plants.

## **Oversight of human clinical trials**

Clinical trials involving human somatic cell gene therapy are overseen by Human Research Ethics Committees (HREC) and/or the Therapeutic Goods Administration (TGA), who must consider patient safety and efficacy. All human clinical trials in Australia must be conducted under either the Clinical Trial Notification (CTN) scheme, involving a HREC reviewing the trial and notifying TGA, or the Clinical Trial Exemption (CTX) scheme, involving the TGA reviewing the trial, which may not proceed until approval is granted. The choice of which scheme to follow lies firstly with the sponsor and then with the HREC that reviews the protocol. The CTX scheme may be more appropriate where the experimental protocol introduces new technology, new material or a new treatment concept which has not been evaluated previously in clinical trials in any country, including 'first in man' trials. Further information about clinical trials in Australia is available on the TGA website, <<http://www.tga.gov.au/ct/index.htm>>.