Australian Government
Department of Health
Office of the Gene Technology Regulator

Celebrating 20 Years of OGTR 2001 - 2021

# Retrospective report 2

## Changing research landscape

21 June 2021

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# Changing research landscape

Over the past twenty years, the field of gene technology has seen many exciting developments, some of which could not have been imagined when the Act was written. A few months before the Act came into effect in 2001, a Parliamentary Library research paper on governance issues relating to GMOs noted that biotechnology was 'changing at such a rapid pace that developments could not possibly be anticipated nor legislated against' (Polya 2001).

## Changes in techniques used in GMO research

Since the structure of DNA was first established in 1953[1], the field of genetics has advanced at speed. The first GMO was created in 1973, the first genome sequence of an organism was completed in 1977, and the first product created using gene technology (human insulin) was approved for commercial release in the USA in 1982[2]. Australian scientists and organisations have been involved in genetic research and regulation since the early days of gene technology.

Over the last twenty years, molecular biology techniques and equipment have become more accessible and affordable. Age is no barrier to science, and GM kits in schools are mainstream. Classroom biology tends to involve bacteria with a long history of safe use. Community scientists have also entered the arena, taking advantage of the accessibility of do-it-yourself biology.

In gene technology research, new tools are now being used to enable scientists to insert, remove or alter the activity of one or more genes, or parts of genes, to modify organisms. Gene editing is making it quicker and easier to modify genomes. In 2016, Dr Raj Bhula, the Regulator, described the advances in GM techniques as 'rapid over the last few years', adding that 'the new techniques are often more specific, more targeted and cheaper than conventional genetic modification techniques' (DoH 2016:11).

One tool used for gene editing, that allows the DNA to be cut in a specific location, is CRISPR (clustered regularly interspaced short palindromic repeats), which is based on a defence system used by bacteria to protect themselves from viral infection.

Gene editing with site-directed nuclease (SDN) techniques introduces a break in an organism's DNA sequence. The break is then repaired, in the process introducing a change in the DNA sequence – this change might involve a small sequence change or the insertion of new sequences.

Gene silencing with RNA interference technology uses short RNA molecules to bind to messenger RNA of target genes. This leads to degradation or inhibition of translation of the target mRNA.

## Changes in focus of research in applications

### DIR applications

Genetically modified organisms are licenced for use in agriculture, as crop plants and vaccines for livestock; and in health and medicine. In 2020, GM microalgae were approved for cultivation trials for the first time.

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1 https://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/BN/0809/ChronGeneticEngineeringA

2 https://americanhistory.si.edu/collections/search/object/nmah_1000967

### *Plants*

The three GM crops grown commercially in Australia are cotton, canola and safflower. The Regulator has also approved GM carnations for growing or importing into the country.

The agronomic traits that were introduced into early GM field crops in Australia were mainly insect resistance and herbicide tolerance. Insect resistant cotton had already been grown commercially since 1996 under GMAC guidelines, when the Act commenced. The first DIR licences approved under the new regulatory system were for varieties of cotton, which had been modified by the introduction of genes from common bacteria (DoHA 2002a:9). In 2003, GM canola varieties were first approved for commercial release (Figure 1).

Early plant licences tended to be for plants containing traits intended to provide production benefits to the farmer, such as improved:

- tolerance to abiotic stresses
- pest and disease resistance, and
- agricultural management of crops.

In the early 2000s, field trials of GM traits were conducted in a wide range of plants, including fruits (grapes, papaya, pineapple), grains (rice, wheat), forage crops (white clover), oilseed crops (canola, cotton, Indian mustard, poppy) and flowers (carnation, rose, torenia). However, of these, only GM canola and cotton have been commercialised to date.

Cotton and canola also remain the predominant parent organisms for approved DIR licences, with 50 and 18 licences issued in the past 20 years, respectively. Today, more than 99.5% of the cotton grown in Australia is genetically modified (GM cotton factsheet) and about 20% of the national canola crop is genetically modified (GM canola factsheet).

In addition to agronomic traits, recent years have seen an increase in the variety and complexity of genetic modifications in crop plants, for example:

- canola modified for altered omega-3 oil content by the introduction of seven genes involved in metabolism of long-chain polyunsaturated fatty acids,
- forage crops with altered nutritional properties to improve digestibility, and
- safflower modified for high oleic acid composition, which has both industrial and food applications.

### *Human therapeutics*

In general, the 20 years since the introduction of the Act have seen an increased focus in applications of GM techniques for human therapeutics, i.e. vaccines and gene therapies.

In 2016, the OGTR noted ‘an increase in the number of human therapeutics that advanced from testing and clinical trial stages to commercialisation’ (DoH 2016:11). This trend reflects what the Regulator called ‘a very pertinent application of gene technology’ (DoH 2016:11).

Currently approved GM human therapeutics for commercial release under DIR licences include:

- vaccines using GM viruses (for Japanese encephalitis, influenza, dengue fever and COVID-19)
- a vaccine using GM bacteria (for cholera), and
- a GM virus therapy for the treatment of melanoma.

### *Animal vaccines*

One animal vaccine has been approved for commercial release in Australia: GM bacteria protecting chickens from disease caused by *Escherichia coli* infection.

Approved animal vaccine trials have tested GM viruses in cattle, chickens, crocodiles and horses.

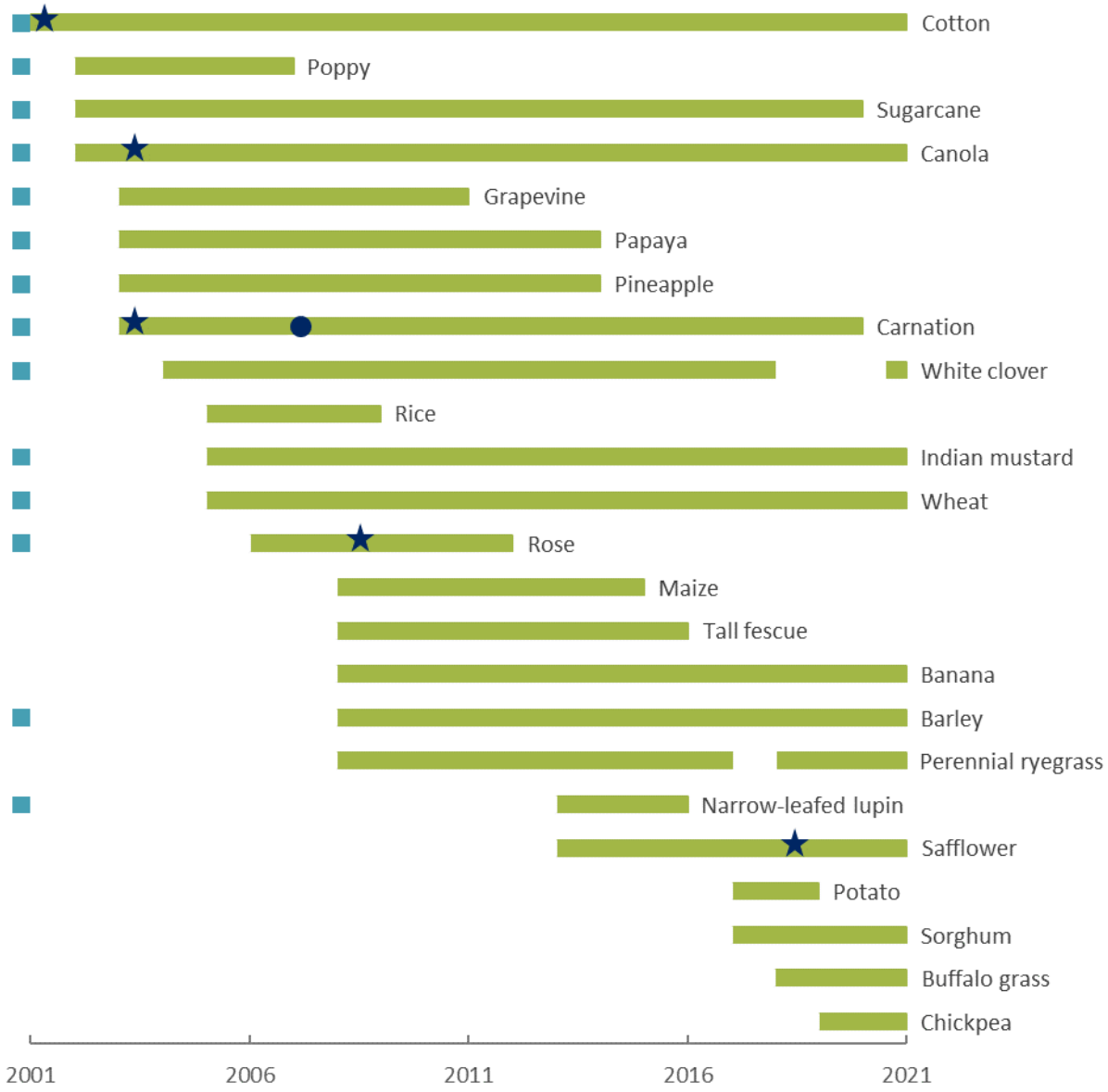


**Figure 1. Plant species for which GMOs have been approved for release under DIR licences. Solid bars, years that a species was approved for release under a DIR licence or on the GMO Register; teal squares, species was approved previously under the GMAC system; blue star, first year a GMO of this species was approved for commercial release; blue circle, first year a GMO of this species was entered onto the GMO Register.**

## DNIR applications

Work in contained facilities primarily examines human disease and disease treatment. At the end of May 2020, 146 DNIR licences were current. Of these, 118 or 81% were for medical applications of gene technology. This illustrates an expanding use of biotechnology for research into human diseases, including genetic treatments (DoH 2019:10).

The rate of development in human therapeutic applications is highlighted in a comment from the Senate inquiry into the Gene Technology Bill 2000 that living GMOs had 'yet to be introduced for

therapeutic use in humans, however, it is claimed that they have the potential to provide vaccines for cholera, malaria and HIV, and treatment for cancer and diabetes' (Commonwealth of Australia 2000:17).

Today, research is increasingly being translated, with over 50% of DNIR licences currently being issued for clinical trials (Figure 2). Vaccines, gene therapies and cancer treatments are the predominant types of therapeutics authorised under DNIR licences for clinical trials (Figure 3). The coronavirus pandemic prompted a surge in clinical trial applications for COVID-19 vaccines.

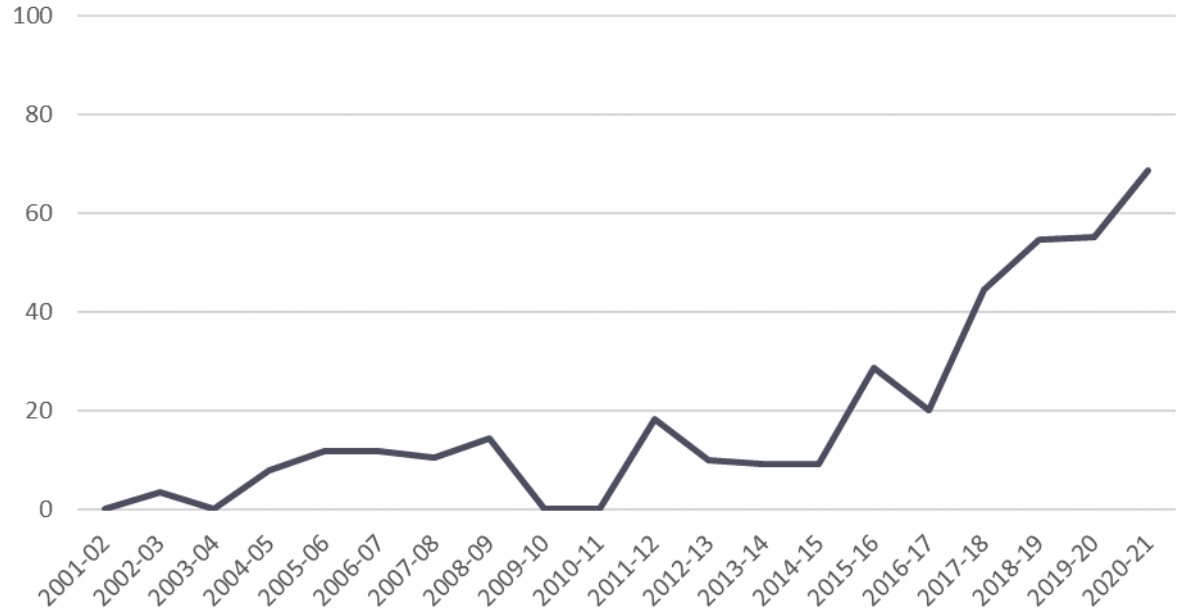


**Figure 2. Clinical trials as a percentage of all DNIR licences issued per year.**

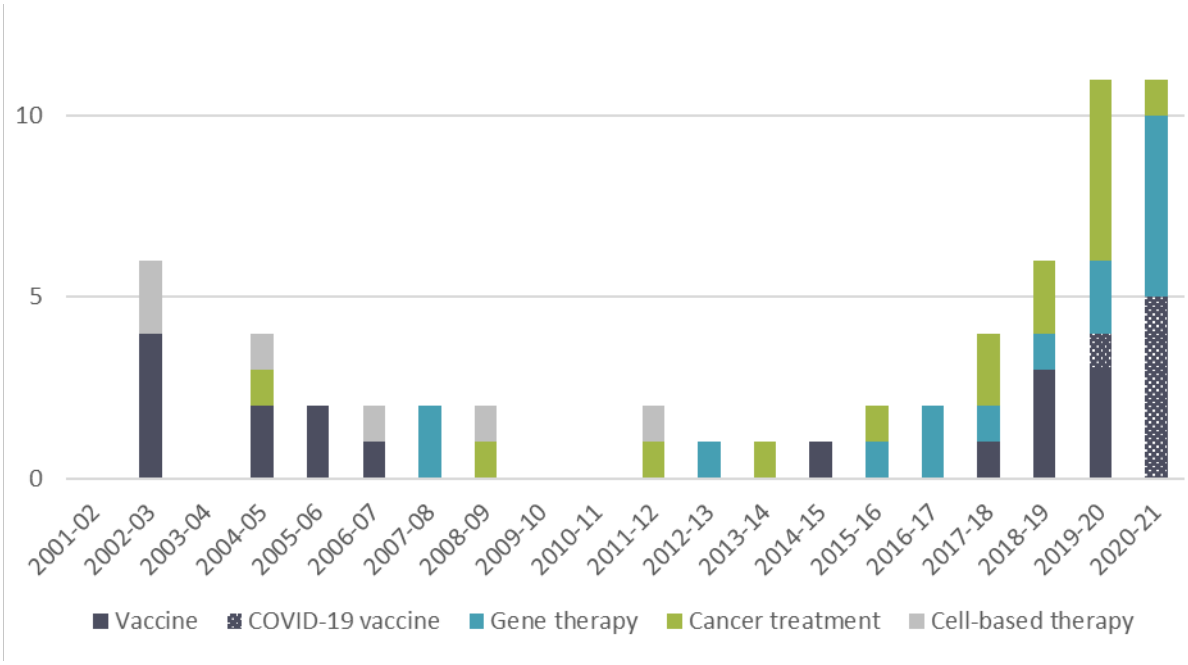


**Figure 3. DNIR licences for clinical trials by application type, as at the end of May 2021.**

## Organisations working with GMOs

A range of organisations work with GMOs in Australia. These can be grouped into the following broad categories:

- Public and private companies
- Universities
- Medical research institutes
- Health services and hospitals
- Government agencies, including CSIRO.

Companies have held over half of all DIR licences issued in the past twenty years, with the remaining licences issued to CSIRO, universities and other government agencies (Figure 4). All commercial DIR licences are held by companies.

As the focus of work conducted under DNIR licences is often related to medical research, DNIR licences have been predominantly (~40%) held by universities (Figure 5). In the past few years, however, there has been a shift, with over half of DNIR licences now being issued to companies. This reflects a recent increase in clinical trials for GM vaccines, gene therapies and cancer treatments.

Most certified facilities are Physical Containment level 2 (PC2; Figure 6). Only four facilities are certified at the highest level of PC4.

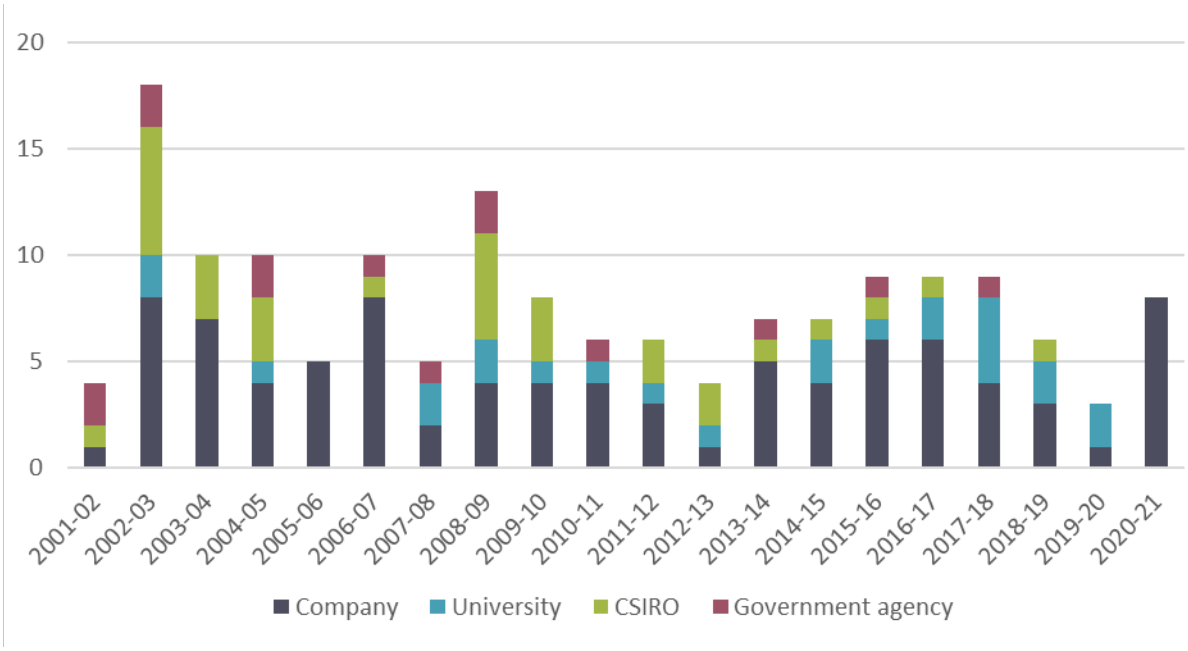


**Figure 4. DIR licences by organisation type, as at the end of May 2021.**

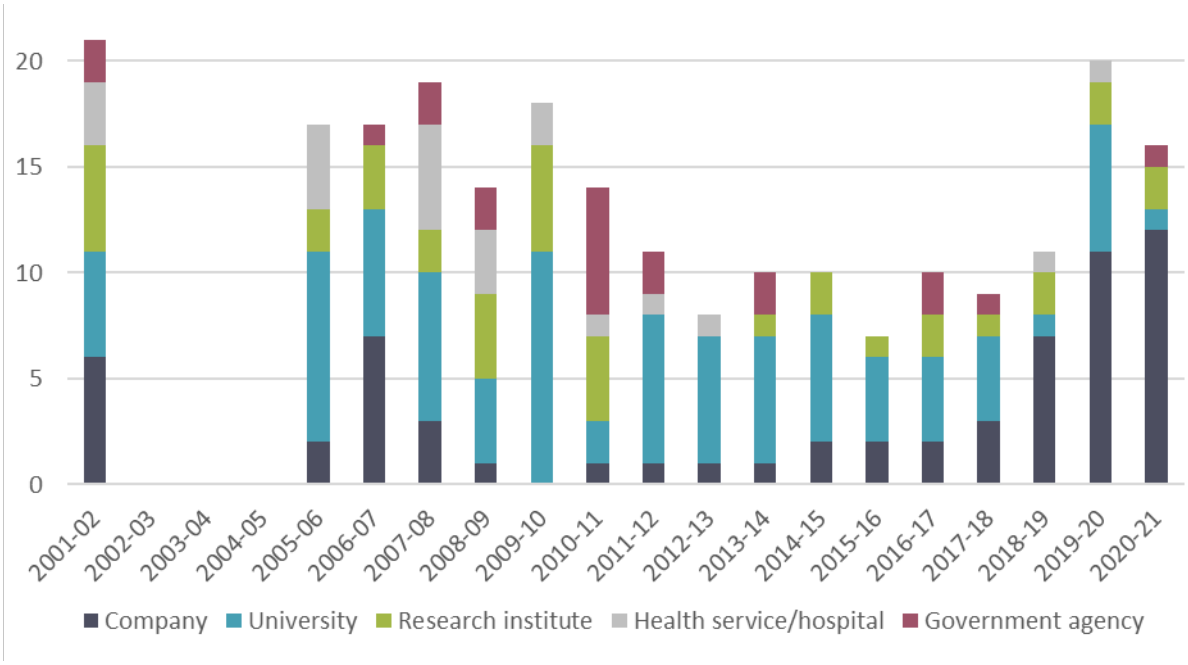


**Figure 5. DNIR licences by organisation type, as at the end of May 2021. The years 2002-03, 2003-04 and 2004-05 are omitted for scale, as over 50 applications were received per year due to the transition from the voluntary to legislative scheme.**

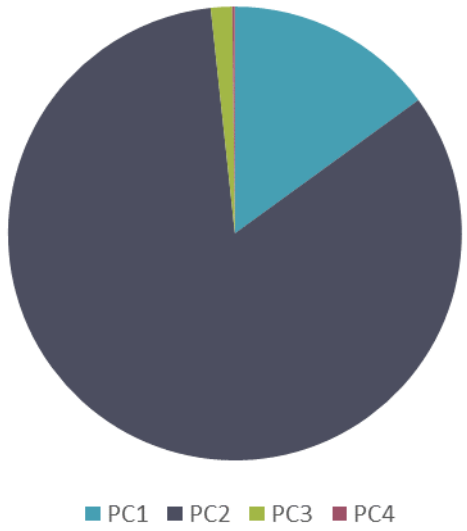


**Figure 6. The predominant level for Physical Containment (PC) facilities is PC2.**

## Adapting to changes in the GMO research landscape

The rapid pace of change in gene technology is accompanied by changes in public attitudes to GMOs, as well as an accumulation of experience with certain types of GMOs that have been available commercially for many years.

As gene technology evolves, regulation needs to keep up with the changes and ongoing challenges of progress. The OGTR keeps an eye on new methodologies and applications, and considers how these fit within legislative definitions. The aim is to ensure that the legislation adequately captures and regulates new technologies, to protect the health and safety of people and to protect the environment.

In the reporting period of 2016–17, the Regulator highlighted the need to review legislation in light of rapid advances in genetic modification techniques. She cited 'those techniques often referred to as genome editing (e.g. site-directed nuclease techniques utilising CRISPR/Cas9 and oligonucleotide-directed mutagenesis)' as being of concern with respect to the clarity of their coverage by the legislation (DoH 2017:12).

In 2017–18, the LGFGT's Third Review of the scheme looked at how modern technology's advances and extensions call for a redefining of practices and their regulation. For example, some variations of SDN techniques clearly fall under the scope of the Gene Technology Act, whereas others can give rise to changes in an organism's genome that are the same as changes introduced using 'conventional' mutagenesis techniques.

Following extensive consultation, the Gene Technology Regulations 2001 were amended in 2019 to clarify the scope of regulation. Organisms modified using SDN-1 techniques, i.e. site-directed nuclease activity with unguided DNA repair, are not GMOs for the purposes of the Act.

Other complex applications that the Third Review considered include synthetic biology, human gene therapy, GMOs released into the broader environment and gene drives (which spread through a population faster than genes with standard Mendelian inheritance). The investigation explored the ongoing regulation of these applications, as well as options to manage possible risks associated with their use (DoH 2018a:11–12).

Reviews and amendments to the Act and Regulations are discussed further in Retrospective report 4.

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# Shortened forms

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|---|---|
| DIR | dealing involving intentional release into the environment |
| DNIR | contained dealing with GMO not involving intentional release into the environment |
| EDD | emergency dealing determination |
| GM | genetically modified |
| GMAC | Genetic Manipulation Advisory Committee |
| GMO | genetically modified organism |
| GTECCC | Gene Technology Ethics and Community Consultative Committee |
| GTMC | Gene Technology Ministerial Council |
| GTMM | Gene Technology Ministers' Meeting |
| GTTAC | Gene Technology Technical Advisory Committee |
| IBC | Institutional Biosafety Committee |
| IOGTR | Interim Office of the Gene Technology Regulator |
| LGFGT | Legislative and Governance Forum on Gene Technology |
| NLRD | notifiable low risk dealing |
| OGTR | Office of the Gene Technology Regulator |
| PC | physical containment |
| RAF | Risk Analysis Framework |
| RARMP | risk assessment and risk management plan |
| Regulator | Gene Technology Regulator |