GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE

COMMUNIQUE
No. 11

This is the eleventh communique of the Gene Technology Technical Advisory Committee (GTTAC). It covers matters considered at the eighteenth and nineteenth meetings of GTTAC, held on 19–20 November 2003 and 18 December 2003 respectively.

GTTAC is a statutory advisory committee to the Gene Technology Regulator (the Regulator) and the Gene Technology Ministerial Council. All Committee members and expert advisers hold office on a part-time basis.

The Regulator receives input from GTTAC on applications for licences to conduct dealings with genetically modified organisms (GMOs), as well as comments on the Risk Assessment and Risk Management Plan (RARMP) that is prepared for each of these applications.

The purpose of this Communique is to provide a brief overview of the applications and RARMPs considered by GTTAC and the advice the Committee has provided to the Regulator with regard to those applications and RARMPs.

The Communique also provides an overview of any other major issues discussed by GTTAC.

Dealings Not Involving the Intentional Release of Genetically Modified Organisms

Dealings Not Involving the Intentional Release of GMOs (DNIRs) are dealings that are usually undertaken within a certified facility (so that the organism is physically contained) and where the personnel involved in the dealing have been assessed as having adequate training and experience for the task. These are typically laboratory-based projects.

Applications and RARMPs for the following DNIRs were assessed:

Application Number and Title	Project Description	GTTAC Comments
DNIR 266/2003 Construction of influenza viruses by reverse genetics for diagnostic and research purposes.	The aim of this project is to employ a technique known as reverse genetics to produce influenza viruses synthetically in order to derive potential influenza virus vaccine candidates in a more rapid and reproducible manner.	GTTAC agreed that the risk assessment identified all the risks associated with the proposed dealings and that the measures proposed in the risk management plan are adequate to deal with the identified risks. Additionally, the Committee recommmended that details of the laboratory staff to be involved in this dealing be provided.
DNIR 271/2003 Investigations on parasite virulence using cross complementation.	The aim of this dealing is to study virulence proteins from parasites.	GTTAC agreed that the risk assessment identified all the risks associated with the proposed dealings and that the measures proposed in the risk management plan are adequate to deal with the identified risks. However, the Committee recommended the applicant provide more detail regarding the housing arrangements for the animals involved in the dealing. The Committee also recommended the licence conditions contain a requirement for the applicant to ensure lab staff are aware of the potential risk associated with this dealing for pregnant women and women likely to become pregnant, and to advise these women not to be involved in the dealing.

DNIR 272/2003 Delivery of replication defective lentiviruses into mice.	The aim of this dealing is to produce defective lentiviral vectors to be introduced into mammalian cell lines and mice.	GTTAC agreed that the risk assessment identified all the risks associated with the proposed dealings. The Committee recommended that screening for replication competent virus generation and minimising the use of sharps will manage the potential risks associated with this dealing in addition to the measures proposed in the risk management plan.
DNIR 273/2003 Repression of hepatic drug metabolism by solid tumours.	The aim of this dealing is to characterise the pathway of down-regulation of CYP3A4 in transgenic mice.	The Committee agreed that the potential risks associated with this dealing can be managed by implementing standard Physical Containment (PC) 2 procedures and minimising the use of sharps while working with recombinant adenoviruses. GTTAC also recommended the applicant clarify the experience of the staff involved in the dealing.
DNIR 274/2003 Experimental infection of *Cules annulirostris, Olerotatus vigilax* and *Culex gelidus* with Japanese encephalitis virus vaccine candidate ChimeraVax™-JE.	The aim of this dealing is to determine if the ChimeriVax™-JE vaccine can infect and replicate in the mosquitoes *C. annulirostris*, *O. vigilax* and *C. gelidus* after oral or intrathoracic infection.	GTTAC agreed that the risk assessment identified all the risks associated with the proposed dealings and that the measures proposed in the risk management plan are adequate to deal with the identified risks.
DNIR 275/2003 Viral protein gene function in whole virus for screening anti-viral compounds.	The aim of this dealing is identify proteins from human viral pathogens that play a role in viral replication.	As for DNIR 274/2003
DNIR 281/2003 Development of *Subterranean clover mottle virus* (SCMoV) as a gene-silencing vector.	This study aims to use *subterranean clover mottle virus* (SCMoV) as a vector for silencing plant genes *in vivo* and *in vitro* experiments.	As for DNIR 274/2003
DNIR 283/2003 Generation of an infectious clone of *Taro bacilliform virus* (TaBV).	The aim of this dealing is to determine whether a single infection with *Taro bacilliform virus (*TaBV) causes alomae disease.	As for DNIR 274/2003.

Dealings Involving the Intentional Release of Genetically Modified Organisms

Dealings Involving the Intentional Release of GMOs (DIRs) are dealings that are undertaken outside of a contained facility. DIRs involve the limited and controlled release (field trial) of a GMO or a commercial (general) release of a GMO.

RARMPs for licence applications for DIRs are released for public comment as part of the consultation process for these applications. Information on how to obtain copies of applications and RARMPs for DIRs is provided at the end of this document.

Advice on Applications

Advice on Cotton

GTTAC considered the following application concerning the release of transgenic cottons in Australia and provided advice on issues to be considered in the preparation of the associated RARMP.

- **Agronomic assessment and seed increase of transgenic cottons expression insecticidal genes from *Bacillus thuriengiensis* (DIR 044/2003)**

  The OGTR has received an application from Dow AgroSciences Australia Limited for the limited and controlled release of GM cotton containing insecticidal genes (chimeric *cry1Ac* and *cry1Fa*) toxic to lepidopteran caterpillar pests of cotton, and a herbicide tolerance marker gene (*pat*). The small scale trial is proposed to occur over a total of 10 hectares over two summer and two winter cotton growing seasons (May 2004 – May 2006) in cotton growing regions of Queensland (Qld), New South Wales (NSW) and in the Northern Territory.

  The aims of the proposed release are to test the efficacy of the two-gene insecticidal cotton line (Widestrike™) against lepidopteran caterpillar pests of cotton as compared to its two parental lines, one introducing the chimeric *cry1Fa* gene or the other introducing the chimeric *cry1Ac* gene, and to evaluate their respective agronomic performance in a range of Australian cotton growing regions. All three lines contain a herbicide tolerance marker gene that confers tolerance to the herbicide glufosinate ammonium.

  The applicant also aims to collect data to develop insect resistance management plans. In addition, the applicant intends to measure the expression levels of the insecticidal proteins in cotton leaves and roots and residues of these proteins in soil, as well as to test the effect of GM cotton lines on non-target organisms. Seed would also be retained for potential future releases. None of the cotton plants from the release, or their by-products, would be used for animal feed or human food.

  GTTAC discussed this application and advised the Regulator that the following issues should be considered in the preparation of the RARMP:

  - The risks posed by DIR 044/2003 are similar to those posed by previous cotton applications;
  - Advice provided in relation to previously assessed GM cottons should be considered in the preparation of the RARMP for DIR 044/2003;
  - The applicant should be requested to provide data on levels of expression under Australian field conditions at the completion of the four seasons of field trials; and

- The applicant should be asked to provide details of the CRY protein expression levels and the lethal dose delivered by the GM plants.

Advice on vaccines

GTTAC considered the following applications concerning the release of vaccines containing transgenic adenoviruses in Australia and provided advice on issues to be considered in the preparation of the associated RARMPs.

- **Development of Porcine adenovirus (PAV) vaccine vectors (DIR 045/2003)**

The OGTR received a licence application from Imugene Ltd for a licence for the limited and controlled release of GM pig adenoviruses. The application proposes the use of up to three sites of PC1 animal house facilities in Victoria (Vic) and the inoculation of up to 200 pigs.

The proposed trial involves four GMOs that have each been modified by introducing one of two pig genes under the control of one of two promoters. The pig genes produce different proteins, known as interferon gamma (IFN-?) and interleukin 5 (IL-5), that play roles in regulating the immune system of pigs.

Pigs raised in commercial production facilities are exposed to a range of organisms that may cause low grade infections that adversely affect their general health and production. To counteract this, antibiotics is sometimes added to pig feed. If the research is successful, the inoculation of pigs with the modified virus may provide an alternative to the use of antibiotics in commercial pig meat production.

Pigs will be inoculated via intranasal or oral routes or by subcutaneous injection, with one or more of the GM viruses. None of the pigs from the trial, or their by-products, will be used for animal feed or human food. Following each trial, inoculated pigs will be euthanased and all animal material disposed of under strict conditions that would destroy the GMOs.

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has regulatory responsibility for veterinary medicine use in Australia, including the registration of vaccines. Data from this proposed trial on the effectiveness of the treatment is necessary before the APVMA could evaluate an application for registration of the GM viruses as products for veterinary use. Further information about the APVMA can be obtained from www.apvma.gov.au.

The Committee advised the Regulator that the applicant should be asked to provide further information regarding:

- The potential for transmission of the GM viruses by insects and whether insects could be excluded from the PC1 animal house;
- Whether the porcine and avian adenoviruses use the same receptors as human adenoviruses;
- Whether expression of the cytokines may increase the pathogenicity or virulence of the GM viruses or a subsequent challenge pathogen; and
- The waste disposal procedures to be used.

GTTAC also advised the Regulator that the applicant should be asked to provide evidence that:

- The GM viruses cannot enter or replicate in human cells; and

- The cytokines are not functionally active in human cells.

- **Development of Fowl adenovirus (FAV) vaccine vectors (DIR 046/2003)**

The OGTR received a licence application from Imugene Ltd for the limited and controlled release of GM fowl adenoviruses (vaccine) which have been modified by the addition of a chicken interferon gamma gene (*ChIFN-g),* that encodes an immuno-regulatory protein. Imugene proposes to carry out multiple limited and controlled releases, within PC1 animal containment facilities in Victoria, from the time of issuing the licence until December 2006.

Inoculation with the GM fowl adenoviruses is expected to stimulate the chickens' immune systems, with a view to replacing the use of antibiotics in chicken feed. Data on the efficacy of the treatment would be necessary for registration of the GM fowl adenoviruses by the APVMA. APVMA approval would be required for these GMOs to be used for inoculation of chickens on a larger scale or outside of contained research facilities. Further information about the APVMA can be obtained from www.apvma.gov.au.

Up to 5000 chickens will be inoculated with the GM viruses. None of the chickens or their by-products, would be used for animal feed or human food. Following each trial, inoculated chickens will be euthanased and all animal material disposed of under strict conditions that would destroy the GMOs.

GTTAC advised the Regulator that the applicant should be asked to provide further information regarding:

- The potential for transmission of the GM viruses to wild birds and the steps that will be taken to prevent this;
- The effects of the transgenes on the immune system of wild birds;
- The methods to be used for waste disposal, particularly of bird litter;
- The possible effects of maternal antibody on trial results;
- Whether expression of cytokines may increase the pathogenicity or virulence of the GM viruses or a subsequent challenge pathogen;
- The potential for increased pathogenicity in the GM viruses from the genetic modification;
- Whether the porcine and avian adenoviruses use the same receptors as human adenoviruses;
- The waste disposal procedures to be used; and
- The relationship between the GM fowl adenoviruses in the trial and commercially available non-GM vaccine strains, and the conventions of the latter's use in industry.

The Committee also advised the Regulator that the applicant should be asked to provide evidence that:

- The GM viruses cannot enter or replicate in human cells; and
- The cytokine is not functionally active in human cells.

Advice on RARMPs

Advice on Canola

GTTAC considered the RARMPs prepared in response to the following applications concerning the release of GM canola in Australia:

- **General release of Roundup Ready (*Brassica napus)* in Australia (DIR 020/2002)**

  The OGTR received an application from Monsanto Australia Ltd (Monsanto) for a licence for the intentional release of GM Canola that has been modified to tolerate glyphosate, the active ingredient in the herbicide Roundup®. The use of Roundup Ready® canola will allow the application of glyphosate for the control of weeds which emerge following crop planting. A parallel application for registration for the use of Roundup® on Roundup Ready® canola was made to the Australian Pest and Veterinary Medicines Authority (APVMA). The APVMA is responsible for the registration of agricultural chemicals for use in Australia.

  Monsanto proposes the commercial cultivation of Roundup Ready® canola in all current and future canola growing regions of Australia, which potentially includes NSW, Vic, Qld, South Australia (SA), Western Australia, Tasmania and the Australian Capital Territory. Release of Roundup Ready® canola requires State or Territory government approval where various moratoria regarding GM crops have been imposed.

  The canola plants and their by-products, would be used in the same manner as conventional canola, including for human food and animal feed. The use of oil derived from Roundup Ready® canola was approved by Food Standards Australia New Zealand in November 2000.

  GTTAC discussed the RARMP and supporting information at length and agreed that this GMO is as safe to human health and safety and the environment as conventional canola. However, during the comprehensive discussion members raised concerns relating to the practical use of Roundup Ready® canola and Roundup® herbicide. These concerns included the potential impact the introduction and management of Roundup Ready® canola may have on herbicide usage and the development of herbicide resistance. The Committee discussed the use of non-glyphosate herbicides on GM volunteers in non GM canola crops, and management of roadside volunteers resulting from seed spillage. The Committee recognised that these concerns were being considered by the APVMA as the responsible regulatory authority.

  The Committee resolved to write to the APVMA outlining their concerns regarding the potential for development of herbicide resistance as a result of inappropriate herbicide use following the introduction of Roundup Ready® canola.

  GTTAC advised the Regulator that:

  - The Committee agrees with the risk assessment made by the OGTR, including the conclusions of the RARMP;
  - The section on Toxicity and Allergenicity should clearly indicate that there is no difference between the GM and non-GM plants, except for the expressed genes;
  - The RARMP should adequately explain why the main areas of concern identified by GTTAC (potential development of herbicide resistance) do not fall under the Gene Technology Act; and

- The Committee agrees with the proposed licence conditions;
- The RARMP should include information on current industry standards for the proximity of seed crops to commercial crops.

- **Field trial – Seed increase and field evaluation of hybrid herbicide tolerant genetically modified canola (DIR 032/2002)**

  The OGTR received an application from Bayer CropScience Pty Ltd (Bayer) for a licence for the limited and controlled release (field trial) of GM canola (*Brassica napus* L) into the environment. The aim of the proposed release is to conduct breeding trials of the GM canola to develop lines that are suitable for the Australian conditions and to produce seed for future releases. The proposed release would occur at 6 sites in 6 different locations per year for 3 years covering a maximum area of 22 ha per year in Vic, SA and NSW.

  Bayer has developed a novel breeding system, based on GM male sterile (MS) and fertility restorer (RF) lines to emulate the natural phenomenon of hybrid vigour. The MS *barnase* gene is derived from the bacterium *Bacillus amyloliquefaciens*. The enzyme encoded by this gene prevents pollen production, thus conferring male sterility. The RF *barstar* gene is also derived from *B. amyloliquefaciens* and encodes a protein that inhibits the Barnase enzyme produced in the MS line. Crosses of the MS lines with the RF lines ensure the production of fertile hybrids. It is this resultant hybrid seed that is employed in agricultural production.

  The MS and RF lines have also been modified to confer tolerance to a herbicide. The herbicide tolerance trait may be used to control weeds in the canola crop. The GM canola also contains regulatory sequences that control the expression of the inserted genes. Bayer has sought and received approval for detail of the origin and identity of the herbicide tolerance gene and regulatory sequences declared as CCI. However, this information was made available to GTTAC and other prescribed expert authorities that were consulted on the preparation of the RARMP.

  The Committee advised the Regulator that:

  - The Committee agrees with the risk assessment made by the OGTR and the conclusions of the RARMP; and
  - The Committee agrees with the proposed licence conditions, with one minor correction required to clarify that deep tillage is not permissible.

Gene Technology Ethics Committee (GTEC) Paper

The Committee was asked to comment on a paper prepared by a GTEC working group on ethical issues associated with transkingdom gene transfer. The Committee discussed the paper and provided a number of suggestions for the final version of the document. Further information regarding the operations of the GTEC are available from the OGTR website.

Review of the *Gene Technology Regulations 2001* (Regulations)

The Committee was provided with an overview of New Zealand's *Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 2003* which are similar to Australia's regulations for exempt and notifiable low risk dealings.

The Committee advised the Regulator that the approach adopted by New Zealand to regulate low risk dealings with GMOs warranted further consideration while reviewing Australia's Regulations.

Enquiries and Risk Assessment and Risk Management Plans

For all enquiries and to obtain copies of applications or RARMPs for dealings involving the intentional release of GMOs into the environment, please phone the OGTR Free-call hotline on 1800 181 030. The RARMPs are also available electronically from our website at http://www.ogtr.gov.au/publications/riskassessments.htm

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