Australian Government
Department of Health
Office of the Gene Technology Regulator

Licence for dealings involving an intentional release of a GMO into the environment

Licence No.: DIR-132

Licence holder: Amgen Australia Pty Ltd

Commercial supply of a tumour-selective genetically modified virus for cancer therapy

Issued: 12 August 2015

More information about the decision to issue this licence is contained in the Risk Assessment and Risk Management Plan prepared in connection with the assessment of the application for the licence. This document can be obtained from the Office of the Gene Technology Regulator website, or by telephoning the Office on 1800 181 030.

Gene Technology Regulation in Australia

Australia's gene technology regulatory system operates as part of an integrated legislative framework. The *Gene Technology Act 2000* (Cth) and corresponding state and territory legislation form a substantial part of a nationally consistent regulatory system controlling the development and use of genetically modified organisms (GMOs).

This licence is issued by the Gene Technology Regulator in accordance with the *Gene Technology Act 2000* and, as applicable, Corresponding State Law.

The Gene Technology Regulator is required to consult with, and take into account advice from, a range of key stakeholders, including other regulatory authorities, on risks to human health and safety and to the environment in assessing applications for dealings involving the intentional release of GMOs into the Australian environment.

Other agencies that also regulate GMOs or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, National Industrial Chemicals Notification and Assessment Scheme and the Department of Agriculture. Dealings conducted under any licence issued by the Regulator may also be subject to regulation by one or more of these agencies. It is recommended that the licence holder consult the relevant agency (or agencies) about their regulatory requirements.

The licence authorises the licence holder and persons covered by the licence to conduct specified dealings with the genetically modified organism(s) listed in Attachment A of this licence. Dealings permitted by this licence may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

Section 1 Interpretations and Definitions

1. In this licence:

   a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;

   b) words importing a gender include any other gender;

   c) words in the singular include the plural and words in the plural include the singular;

   d) words importing persons include a partnership and a body whether corporate or otherwise;

   e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

   g) specific conditions prevail over standard conditions to the extent of any inconsistency.

2. In this licence:

'Act' means the *Gene Technology Act 2000* (Cth) or the corresponding State legislation under which this licence is issued.

'Annual Report' means a written report provided to the Regulator within 90 days of each anniversary of issue of this licence containing all the information required by this licence to be provided in the Annual Report.

'ARTG' means the Australian Register of Therapeutic Goods.

'Dealings' in relation to the GMO, means the following:

   a) import the GMO; and

   b) transport the GMO; and

   c) dispose of the GMO;

and includes the possession (including storage), supply or use of the GMO for the purposes of, or in the course of, a dealing mentioned in any of paragraphs (a) to (c).

'GM' means genetically modified.

'GMOs' means the genetically modified organisms the subject of the dealings authorised by this licence.

'GM virus' means GM *Herpes simplex virus 1* known as Talimogene laherparepvec.

'OGTR' means the Office of the Gene Technology Regulator.

'Personal Information' means information or an opinion (including information forming part of a database), whether true or not, and whether recorded in a material form or not, about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion.

'Regulator' means the Gene Technology Regulator.

Section 2 Licence conditions and obligations

3. This licence does not authorise dealings with GMOs that are otherwise prohibited as a result of the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

4. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.

5. The holder of this licence ('the licence holder') is Amgen Australia Pty Ltd.

6. The persons covered by this licence are the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by this licence.

7. Any person, including the licence holder, may conduct any permitted dealing(s) with the GMO.

Note: Use of the GMO for therapeutic purposes is not regulated under the Gene Technology Act 2000 and this licence neither authorises nor limits such use. The GMO (a live GM virus) is also subject to regulation by other federal and state departments and agencies, including the Therapeutic Goods Administration and the Department of Agriculture. These other departments and agencies may impose further requirements for, or limitations on, these dealings.

8. The only permitted dealings authorised by this licence are to:

   a) import the GMO; and

   b) transport the GMO; and

   c) dispose of the GMO;

and the possession (including storage) and supply of the GMOs in the course of any of these dealings.

9. Dealings with the GMO may be conducted in all areas of Australia.

10. The GMO covered by this licence is the GM *Herpes simplex virus 1* Talimogene laherparepvec.

2.1 Obligations of the Licence Holder

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

11. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

12. The licence holder must:

   a) inform the Regulator immediately in writing of:

      i. any relevant conviction of the licence holder occurring after the commencement of this licence; and

      ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; and

iii. any event or circumstances occurring after the commencement of this licence that would affect the capacity of the holder of this licence to meet the conditions in it; and

b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

13. The licence holder must inform any person covered by this licence, to whom a particular condition of this licence applies, of the following:

a) the particular condition (including any variations of it);

b) the cancellation or suspension of the licence;

c) the surrender of the licence.

2.2 Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition requires that any new information that may affect the risk assessment is communicated to the Regulator.

14. The licence holder must inform the Regulator if the licence holder becomes aware of:

a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

b) any contraventions of the licence by a person covered by the licence; or

c) any unintended effects of the dealings authorised by the licence.

Note: The Act requires, for the purposes of the above condition, that:

a) the licence holder will be taken to have become aware of additional information of a kind mentioned in paragraph 14a) if he or she was reckless as to whether such information existed; and

b) the licence holder will be taken to have become aware of contraventions, or unintended effects, of a kind mentioned in paragraph 14b), if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note: Contraventions of the licence may occur through the action or inaction of a person.

15. If the licence holder is required to inform the Regulator under the immediately preceding condition, the Regulator must be informed without delay.

Note: An example of informing without delay is contact made at the time of the incident via the OGTR free call phone number 1800 181 030, which provides emergency numbers for incidents that occur out of business hours. Notification without delay will allow the OGTR to conduct a risk assessment on the incident and attend the location if required.

16. If at any time the Regulator requests the licence holder to collect and provide information about any matter to do with the progress of the dealings authorised by this licence, including but not confined to:

a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14a);

b) any contraventions of the licence by a person covered by the licence, whether or not the licence holder has provided information to the Regulator under condition 14b);

c) any unintended effects of the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14c);

d) research, including by way of survey, to verify predictions of the risk assessment, or for any purpose related to risks to the health and safety of people, or to the environment;

e) scientific literature and reports in respect of the GMO authorised by this licence, for a nominated period;

f) details of any refusals of applications for licences or permits (however described) to deal with the GMO made pursuant to the regulatory laws of a foreign country;

and the request is reasonable, having regard to consistency with the Act and relevance to its purpose, then the licence holder must collect the information and provide it to the Regulator at a time and in the manner requested by the Regulator.

Note: The Regulator may invite the licence holder to make a submission on the reasonability of a request by the Regulator to collect and provide information relevant the progress of the GMO.

2.3 Obligations of persons covered by the licence

17. Persons covered by this licence must not deal with the GMO except as expressly permitted by this licence.

18. If a person is authorised by this licence to deal with the GMO and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Section 3 Reporting and Documentation

3.1 Notification of Authorisation by the Therapeutic Goods Administration

19. If the GMO is included on the Australian Register of Therapeutic Goods (ARTG), the Licence holder must notify the Regulator in writing within 14 days of registration.

20. The licence holder must notify the Regulator in writing of any subsequent amendments to the conditions of the ARTG registration involving the pattern of usage, handling, storage, transport or disposal of the GMO, within 14 days of the change occurring.

3.2 Annual Report

21. The licence holder must provide an Annual Report to the Regulator that includes:

a) Information about any adverse impacts, unintended effects, or new information relating to risks, to human health and safety or the environment caused by the GMOs or material from the GMOs; and

b) Information about the number of the GM virus doses imported and sold for commercial purposes in each State and Territory over the reporting period.

3.3 Testing methodology

22. Prior to conducting any dealings with the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO and the presence of the genetic modifications described in this licence in a recipient organism. The detection method must be capable of reliably distinguishing between GMO described in this licence and the parent organism.

ATTACHMENT A

DIR No: 132

Full Title: Commercial supply of a tumour-selective genetically modified virus for cancer therapy

Organisation Details

Postal address: Amgen Australia Pty Ltd.
Mezzanine Level
115 Cotham Road
Kew, Vic 3101
Australia

Phone No: (03) 9854 9800

IBC Details

IBC Name: Queensland Clinical Trials Network Institutional Biosafety Committee

GMO Description

GMOs covered by this licence:

HSV-1 genetically modified by deletion and insertion of genes and other genetic elements as listed below, known as Talimogene laherparepvec.

Parent Organism:

Common Name: Human herpes virus

Scientific Name: Human *herpes simplex virus 1* (HSV-1), strain JS1

Modified traits:

Categories: human therapeutic – attenuation, enhanced immune response

Description: Talimogene laherparepvec is a live attenuated HSV-1 (strain JS1), modified to selectively replicate in tumours (rapidly dividing cells) and illicit an immune response. It was generated by a series of *in vitro* homologous recombination events in cultured cells co-transfected with viral DNA and plasmid shuttle vectors carrying fragments of the viral genome with the desired modifications.

Genetic elements responsible for conferring the modified traits:

Gene deletion: Deletion of both copies of the Infected Cell Protein 34.5 gene (*ICP34.5*).

Gene deletion: Deletion of Infected Cell Protein 47 gene (*ICP47*).

Gene insertion: Insertion of two copies of human Granulocyte-Macrophage Colony-Stimulating Factor (*hGM-CSF*) in place of the deleted *ICP34.5* genes.

Promoter: Expression of the *hGM-CSF* genes are driven by the non-coding viral IE1 promoter/enhancer from cytomegalovirus (CMV).

Terminator: Bovine growth hormone polyadenylation signal sequence (bgh-PolyA) is used to achieve polyadenylation of the hGM-CSF mRNA

Purpose of the dealings with the GMO

Commercial release of Talimogene laherparepvec for the purpose of import, transport, storage and disposal for the purpose of its commercial supply as a therapeutic product.