Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

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

Licence No.: DIR 140

Licence holder: Novotech (Australia) Pty Ltd

Title: Clinical trial of a genetically modified virus for treatment of liver, kidney and prostate cancer

Issued: 10 March 2016

Varied: 19 March 2018

Varied: 15 May 2020

Transferred to Novotech (Australia) Pty Ltd: 18 March 2021

Varied: 6 March 2023

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 activities involving 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, Australian Industrial Chemicals Introduction Scheme and the Department of Climate Change, Energy, the Environment and Water. 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 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.

Further information on licence DIR 140

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 (OGTR) website or by telephoning the Office on 1800 181 030.

Section 1 Interpretations and definitions

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.

In this licence:

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

'Analytical facility' means a laboratory or premises that perform testing and/or analysis on biological samples (e.g. blood, tissue, cells, proteins, nucleotides) in Australia.

'Annual Report' means a written report provided to the Regulator by the end of September each year, containing all the information required by this licence to be provided in the Annual Report for the preceding financial year.

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

(a) import the GMO;

(b) transport the GMO;

(c) conduct experiments with the GMO;

(d) dispose of the GMO;

and includes the possession, 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 (d).

'Destroy', (or **'Destroyed'** or **'Destruction'**) means, as the case requires, killed by one or more of the following methods:

(a) treatment with chemical disinfectant;

(b) autoclaving;

(c) high-temperature incineration; and

(d) any other approved methods used by Study Sites for disposal of infectious clinical waste.

Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

'Excluded Persons' means:

- women who are known to be pregnant, or who are breastfeeding;
- persons with known significant immunodeficiency due to underlying illness (e.g. HIV/AIDS) and/or immunosuppressive medication;
- persons with an ongoing severe inflammatory skin condition requiring medical treatment; and
- persons with a history of severe eczema requiring prior medical treatment.

'GM' means genetically modified.

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

'ICH-GCP' means the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - *Guidelines for Good Clinical Practice*.

'Material' means non-biological material used in conjunction with the GMO, such as syringes, swabs, vials, gloves or items used for clean-up of spills.

'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.

'Sample' means any biological material collected from trial participants for subsequent analysis.

'Serious adverse event' means any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

'Study Site' means a hospital in Australia at which trial participants are inoculated with the GMO. Study Sites must be registered and licensed for the purposes of handling scheduled medicines and poisons as legislated through the Poisons Standard, and other relevant Australian state or territory laws in effect at the time.

'TGA GCP Guidelines' means the TGA *Note for Guidance on Good Clinical Practice* designated CPMP/ICH/135/95.

'WHO Universal Standard Precautions' means World Health Organisation *Universal precautions for the prevention of transmission of infectious agents in healthcare settings*.

Section 2 General conditions and obligations

1. 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.
2. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.
3. The holder of this licence ('the licence holder') is Novotech (Australia) Pty Ltd.
4. 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.
5. To the extent that any activity by a trial participant may be considered to be a dealing for purposes of the Act, that dealing is authorised by this licence.
6. The only dealings authorised by this licence are to:
   (a) import the GMO;
   (b) conduct the following experiments with the GMO:
      i) administration of the GMO to trial participants by intratumoural injection or intravenous infusion;
      ii) collection of samples that may reasonably be expected to contain the GMO from trial participants; and
      iii) *in vitro* analysis of the samples mentioned in (b)ii)
   (c) transport the GMO;
   (d) dispose of the GMO;

   and possession, storage, supply and use of the GMO in the course of any of these dealings.
7. The experimental dealings may only be conducted between March 2016 and March 2025, unless covered by another authorisation.

Obligations of the Licence Holder

8. The licence holder must immediately notify the Regulator in writing if any of the details of the contact person for the licence change.

   Note: Please address correspondence to ogtr.applications@health.gov.au.

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.

9. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.
10. 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.

The following conditions seek to ensure that persons conducting the dealings are aware of the licence conditions and appropriate processes are in place to inform people of their obligations.

11. Before commencing the clinical trial with the GMO **at each Study Site**, the licence holder must provide the Regulator with:

(a) the names of all organisations and persons, or functions or positions of persons (other than trial participants), who will be covered by the licence at that Study Site, with a description of their responsibilities;

Note: Examples of functions or positions are 'Principal Investigator', 'Clinical research assistant' etc.

(b) details of how the persons covered by the licence will be informed of licence conditions;

Note: This may include training, labelling, contractual agreements with other organisations such as contract research organisations, clinical waste treatment providers and courier companies, etc.

(c) details of how the licence holder will ensure compliance with licence conditions at the Study Site over the period that dealings are being conducted at the Study Site.

Note: This may include a description of any contracts, agreements, or other enforceable arrangements.

12. Any changes to the information required under Condition 11 must be communicated in writing to the Regulator within 14 days of the changes occurring.

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.

Note: Information required under Condition 13 may be provided to contractors who are engaged solely for the transport and/or disposal of the GMOs through labelling the outermost container of the GMOs.

14. Subject to Condition 15, the licence holder must not permit a person covered by this licence to conduct any dealing unless:

    (a) the person has been informed of the licence conditions, including any variation of the licence;

    (b) the licence holder has obtained from the person a signed and dated statement that the person:

        i) has been informed by the licence holder of the licence conditions including any variation of the licence; and

        ii) has understood and agreed to be bound by the licence conditions, or its variations.

    (c) the licence holder has trained the person in a manner which:

        i) enables the person to safely conduct the dealings in accordance with the conditions of this licence; and

        ii) enables the person to meet the work practices and behavioural requirements for conducting the dealings in Medical facilities.

15. The licence holder is not required to comply with any part of paragraph (b) or (c) of Condition 14 in relation to the following classes of person:

    (a) personnel at Analytical facilities;

    Note: The Licence holder must have processes in place to ensure that part (a) of Condition 14 is met in relation to persons conducting dealings in Analytical facilities, and that the Regulator is informed as soon as reasonably possible if there is an unintentional release of the GMO, or if persons undertaking dealings are exposed to the GMOs, at an Analytical facility (as required by Condition 31).

    (b) contractors transporting the GMOs from the point of import directly to a central storage facility or Study Site, provided the consignment is:

        i) clearly labelled to indicate (at a minimum) that it contains GMOs and is authorised under the *Gene Technology Act 2000* through licence DIR 140;

        ii) packaged and transported according to IATA requirements for class UN 3373; and

        iii) only to be transported within Australia from the point of import to the central storage facility (named in, or notified in accordance with, Condition 24) or directly to a Study Site.

    (c) contractors engaged solely for transport and/or disposal of the GMOs within Australia, or for export provided:

        i) the GMOs are double contained; and

        ii) the outermost container is labelled to indicate (at a minimum):

            - that it contains GMOs;
            - the contact details for the Licence Holder; and
            - instructions to notify the Licence holder in case of an unintentional release of the GMOs; and

- where transport is for the purpose of disposal, that the GMOs must be destroyed by autoclaving, high-temperature incineration, chemical treatment or otherwise destroyed as clinical waste.

16. The licence holder must:

    (a) inform the persons covered by this licence that any Personal Information relevant to the administration and/or enforcement of the licence may be released to the Regulator; and

    (b) provide the Regulator, if requested, with copies of the signed and dated statements referred to in Condition 14.

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.

17. 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 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, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

18. If the licence holder is required to inform the Regulator under Condition 17, the Regulator must be informed as soon as reasonably possible.

Obligations of persons covered by the licence

19. Persons covered by this licence must not deal with the GMOs except as expressly permitted by this licence.

20. If a person is authorised by this licence to deal with the GMOs 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 Limits and control measures

Note: This licence does not expressly authorise or prohibit any dealings or storage in certified physical containment facilities. Under the Act it is not an offence to deal with a GMO if the dealing is otherwise licenced or if it is an NLRD or an exempt dealing and it complies with all relevant statutory requirements.

Limits on the release

The following licence conditions maintain the risk assessment context within which the application was assessed by imposing limits on where and when experiments with the GMOs may be performed, and on other activities that can be undertaken.

21. The GMO covered by this licence is JX-594, also known as Pexa-Vec, described in **Attachment A** of the licence.

22. Details of each Study Site must be notified to the Regulator at least 14 days before commencement of dealings at that Study Site.

23. All dealings permitted under this licence must be conducted within Study Sites or Analytical facilities, except for:

    (a) import;

    (b) storage;

    (c) transport; and

    (d) disposal.

24. Prior to distribution to Study Sites within Australia, the GMO may only be stored at Flinders Clinical Trial Services, Adelaide, South Australia or other distribution centres notified to the Regulator in writing at least 7 days prior to the commencement of storage.

25. A maximum of 75 adults with Hepatocellular Carcinoma or Renal Cell Carcinoma or Prostatic Carcinoma may be inoculated with the GMO.

Controls on the Release

The following licence conditions manage the identified risks, and maintain the risk assessment context within which the application was assessed, by restricting exposure to the GMO.

Conduct of the clinical trial

26. The licence holder must ensure that the trial is conducted according to ICH-GCP and TGA GCP Guidelines and WHO Universal Standard Precautions.

27. Before commencement of dealings at each Study Site, the licence holder must ensure that appropriate 'Contact Precautions' are developed to minimise interpersonal transmission of the GMO from patients who present with GMO-related lesion/s to clinical staff and other patients. These precautions must be based on a risk assessment and documented as Standard Operating Procedures (SOPs). Both the risk assessment(s) and SOP(s) must be provided to the Regulator on request.

28. The licence holder must ensure that Excluded Persons are excluded from directly handling the GMO, administering it to patients or caring for trial participants who have or may have GMO-related lesions.

29. The licence holder must ensure that procedures are in place to account for all GMO stocks imported into Australia under this licence. The GMO must be accounted for from import to destruction, and records must be made available to the Regulator on request.

30. The licence holder must ensure that procedures are in place and implemented at each Study Site to track the dispensation, return and destruction of the containers described in Condition 38.

31. If any of the events described in Condition 48 occur, the appropriate procedure(s) from the Contingency Plan must be implemented.

Note: Condition 48 lists events which the Contingency Plan must address, while Condition 49 specifies content for the Contingency Plan.

Conditions relating to trial participants

32. The licence holder and persons administering the GMO must ensure that exclusion criteria used in selecting trial participants include (but need not be limited to) the following:

Exclusion from the trial of persons who:

(a) are Excluded Persons as defined in this licence;

(b) experienced a severe systemic reaction or side effect as a result of a previous exposure to *vaccinia virus*; or

(c) are unable or unwilling to comply with the requirements listed in Condition 34.

33. The licence holder must ensure that persons are not enrolled in the trial without first ascertaining whether or not they are likely to come into contact with children under 12 months of age or Excluded Persons. This must be documented in writing and records made available to the Regulator on request.

33A. If any trial participants were identified under Condition 33 as likely to come into contact with children under 12 months of age or Excluded Persons, the licence holder must ensure that these trial participants are not inoculated with the GMO by intravenous infusion.

34. The licence holder must ensure that trial participants are educated about the potential for transmission of the GMO to untreated people and to animals, about possible adverse effects, about measures to prevent transmission, and about how to recognise that transmission may have occurred, and obtain trial participants' written agreement that:

(a) while undergoing treatment with the GMO, they will implement hygiene measures intended to prevent transmission of the GMO to other people and to animals, including but not limited to frequent hand washing with soap or hand disinfectant, respiratory hygiene and cough etiquette (for two weeks after each round of treatment) and refraining from blood, tissue or organ donation;

Note: People who come into contact with livestock or other animals should wash their hands thoroughly before caring for animals or handling equipment such as food/water bowls, bridles or buckets.

(b) they will avoid direct physical contact with children under 12 months of age and Excluded Persons, from the time of each treatment with the GMO until after the respective follow-up visit to the treating hospital that occurs on or after day 7 post-inoculation;

Note: Direct physical contact means contact of any kind between a trial participant and another indicated person.

(c) should they develop GMO-related lesions during the study, they will, until such time as the lesions have healed:

i) continue to avoid direct physical contact with children under 12 months of age and Excluded Persons;

ii) keep skin lesions covered with a dressing;

iii) treat any item that comes into contact with the lesion or the dressing, including the outer surface of the dressing while in place, as potentially contaminated with the GM virus;

iv) follow instructions provided by the treating hospital (Study Site) for disinfection of contaminated clothing, towels, linens etc (e.g. laundering in hot water with detergent and/or treatment with bleach);

v) if oral lesions are present, wear a mask in the presence of other people or animals and refrain from sharing items such as toothbrushes and eating utensils;

vi) prevent all direct physical contact (by both people and animals) with lesions, dressings, or with any potentially contaminated Material except where necessary for patient care;

Note: Preventing physical contact by animals includes such measures as:

- *preventing animals from sniffing or otherwise contacting a lesion, scab, or dressings, clothing, towels, sheets etc that have been in direct contact with a lesion or scab; and*
- *keeping pets out of the room while changing dressings or clothes, and sealing the used dressing inside a primary and secondary container before allowing the pet back into the room.*

vii) ensure persons caring for lesions wear disposable gloves and wash or disinfect their hands immediately afterwards;

viii) seal used dressings and other Materials used in caring for the lesion in a primary container (e.g. a sealable plastic bag), place these within a secondary container provided by the Study Site, and store the secondary container such that it is inaccessible to children and animals until it is returned to the Study Site;

ix) return the secondary container referred to above, and its contents, to the Study Site for disposal as clinical waste.

(d) if sexually active, prostatic cancer patients must use a condom during treatment and for at least six weeks following the final injection;

(e) used condoms must be handled as used dressings as described in Condition 34 (c) viii) and ix);

(f) prostatic cancer patients will not donate sperm during treatment and for at least six weeks following the final injection; and

(g) they will inform the Study Site as soon as reasonably possible if they suspect that transmission of the GM virus to another person or to an animal may have occurred.

35. Before the clinical trial commences, the educational material and the form of the written agreement referred to in Condition 34 must be submitted to, and approved by, the Regulator.

36. Records of trial participants' agreements as required under Condition 34 must be made available to the Regulator on request.

37. Trial participants must be assessed for the presence of GMO-related lesions at each follow-up visit to the Study Site that occurs on or after day 7 post-inoculation after each treatment with the GMO. If any GMO-related lesion is found, the trial participant must be informed that they have a GMO-related lesion and to continue to avoid children under 12 months of age and Excluded Persons until such time as the clinician determines that the lesion has healed.

38. The licence holder must ensure all trial participants, from the time of inoculation, are provided with a supply of unbreakable secondary containers appropriate for transporting waste back to the Study Site, labelled to indicate that it contains GMOs; that it must be destroyed by autoclaving, high-temperature incineration, chemical treatment or as clinical waste; and with contact details for the Study Site.

Note: Unbreakable means able to withstand all reasonably expected conditions of storage and transport such as: the forces, shocks and impacts expected during handling; or changes of temperature, humidity or air pressure.

Work practices at Study Sites

39. When undertaking a dealing with a GMO at a Study Site, including storage and disposal, persons covered by this licence must employ work practices and behaviours which:

    (a) ensure containment of the GMO; and

    (b) will not pose a risk to the health and safety of people and the environment.

40. For the purposes of Condition 39, the work practices and behaviours must include, but are not limited to, the following:

    (a) all inoculations of the GMO must be administered by suitably qualified and trained medical staff.

    (b) when dispensing and administering the GM virus, clinical trial staff must:

        i) use a Class II biosafety cabinet, or alternative containment equipment approved in writing by the Regulator, to prepare the inoculum;

        ii) wear personal protective equipment including a laboratory coat or gown, gloves, eye protection and mask;

        iii) follow institutional procedures for safe handling of sharps.

    (c) if a trial participant presents at a Study Site with a GMO-related lesion, the 'Contact Precautions' SOPs developed for the Study Site to minimise interpersonal transmission of the GMO from these patients must be implemented.

Note: Contact Precautions SOPs are required for each Study Site by Condition 27.

Patient samples containing the GMO

41. Where a sample taken from a trial participant contains the GMO, or may reasonably be expected to contain the GMO, the sample must be treated as if it were the GMO.

42. Where laboratory analysis of Samples that may reasonably be expected to contain the GMO occurs in Australia, it may only take place in Analytical Facilities.

Storage of the GMO

43. Storage of the GMO at individual Study Sites, Flinders Clinical Trial Services or any other distribution centre notified to the Regulator under Condition 24 must be in accordance with Part 2.1 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs,* as current at the time of storage.

44. Samples that may reasonably be expected to contain the GMO that are stored in Analytical Facilities must be stored under two levels of containment. The outermost container must be unbreakable and clearly labelled to indicate that it contains or may contain a GMO.

Note: In the case of a small storage unit such as a fridge, freezer or liquid nitrogen container, the secondary container may be the storage unit. Unbreakable means able to withstand all reasonably expected conditions of storage such as: the forces, shocks and impacts expected during handling; or changes of temperature, humidity or air pressure.

Transport and Disposal of the GMO

45. Transport of the GMO must be in accordance with Part 1.2 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* in force at the time of transportation, unless:

    (a) the GMO is in its original packaging, in which case the requirement for *Decontamination of Containers* (items 1.2.1.6 and 1.2.1.7 in version 1.1 of these guidelines) is exempted; or

    (b) the transport is by contractors transporting the GMO from the point of import to Flinders Clinical Trial Services or directly to a Study Site, and the transport is in accordance with Condition 15 (b); or

    (c) the transport is by contractors for the purpose of disposal and is in accordance with Condition 15 (c);

    (d) waste potentially contaminated with the GMO is being returned to a Study Site by a trial participant.

46. Decontamination of the GMO or waste containing the GMO must be by autoclaving, high temperature incineration, chemical treatment or any other method approved in writing by the Regulator. Decontamination by commercial waste contractors may be by approved methods in use by Study Sites for the disposal of infectious clinical waste.

47. Unless covered by another authorisation, the GMO and any Material or waste containing the GMO must be destroyed or exported, on or before expiration of the licence.

Contingency Plans

48. Before any trial participant is inoculated with the GMO, a written Contingency Plan must be submitted to the Regulator detailing measures to be taken in the event of:

    (a) the unintentional release of the GMO, such as a spill outside of a Study Site;

    (b) suspected or confirmed transmission to persons other than trial participants;

    (c) suspected or confirmed transmission to animals; and

    (d) a person exposed to the GMO (including a trial participant) developing a severe adverse response, including those known to result from infection with *vaccinia virus*.

49. The Contingency Plan must include details of procedures to:

    (a) ensure the Regulator is notified as soon as reasonably possible after the licence holder becomes aware of the event;

    (b) implement the following measures if there is a spill of the GMO, such as during import, transport, storage or disposal:

        i) contain the GMOs to prevent further dispersal; and

ii) decontaminate the exposed area with an appropriate chemical disinfectant effective against the GMOs.

(c) implement the following measures if transmission of the GMO to people other than trial participants or to animals is suspected:

i) provide appropriate medical or veterinary treatment to affected persons or animals;

ii) take steps to prevent the further spread or persistence of the GMO; and

iii) identify the pathway of exposure.

(d) implement the following measures if a person exposed to the GMO (including a trial participant) exhibits symptoms of a severe adverse response to *vaccinia virus*:

i) provide appropriate medical treatment to the affected person; and

ii) take steps to prevent the spread or persistence of the GMO.

Section 4 Additional Reporting Requirements

Notice of commencement and completion of the trial

50. The licence holder must notify the Regulator of the following:

(a) the first inoculation of the first trial participant at each Study Site, within 7 days of the event; and

(b) the final inoculation of the last trial participant at each Study Site, within 30 days of the decision to cease inoculations at the Study Site.

Annual Report

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

(a) the number of trial participants inoculated with the GMO under this licence in the previous 12 months; and

(b) details of any serious adverse events linked to exposure to the GMOs.

Testing methodology

52. The licence holder must provide the Regulator with a written document describing an experimental method that is capable of reliably detecting the presence of the GMO and the presence of the genetic modifications described in this licence in a recipient organism. The detection method should be capable of reliably distinguishing between the GMO described in this licence and the parent organism. The document must be provided prior to commencing any dealings authorised by this licence.

ATTACHMENT A

DIR No: 140

Full Title: Clinical trial of a genetically modified virus for treatment of liver, kidney and prostate cancer

Organisation Details

Postal address: Novotech (Australia) Pty Ltd
Level 2, 381 MacArthur Ave, Hamilton QLD 4007

Phone No (07) 3719 6000

IBC Details

IBC Name: BioDesk Institutional Biosafety Committee

GMO Description

GMO covered by this licence:

Vaccinia virus (NYCBH strain) genetically modified by insertion of genes and genetic elements listed below, known as pexastimogene devacirepvec (Pexa-Vec; JX-594).

Parent Organism:

Common Name: *Vaccinia virus* (smallpox vaccine)

Scientific Name: *Vaccinia virus*, New York City Board of Health (NYCBH) vaccine strain

Modified traits:

Categories: human therapeutic – attenuation, enhanced immune response, reporter gene expression

Description: Pexa-Vec is a live vaccinia virus (NYCBH vaccine strain), modified so as to enhance its specificity for cancerous (rapidly dividing) cells and elicit an immune response. It was generated by homologous recombination in cultured cells that were infected with the parent virus and transfected with a plasmid carrying a fragment of the viral genome with the desired modification. A single recombinant clone was isolated by plaque purification.

Genes and genetic elements responsible for conferring the modified traits:

Gene disruption: Inactivation of viral *thymidine kinase (TK)* gene.

Gene insertion: Insertion within the viral *thymidine kinase* gene of:

- human Granulocyte-Macrophage Colony-Stimulating Factor (*hGM-CSF*) gene
- bacterial *lacZ* gene from *Escherichia coli*

Promoters: Expression of the *hGM-CSF* gene is driven by the non-coding synthetic *vaccinia virus* early/late promoter.

Expression of the lacZ gene is driven by the *vaccinia virus* p7.5 promoter.

Purpose of the dealings with the GMO:

The purpose of the clinical trial is to assess the effectiveness and safety of the GMO as a treatment for Hepatocellular Carcinoma, Renal Cell Carcinoma or Prostatic Carcinoma when provided in conjunction with a non-viral cancer treatment, compared with the non-viral treatment alone.