Environmental Protection Authority
Te Mana Rauhī Taiao

Staff Assessment Report

Application APP203530

To import and release a genetically modified live-attenuated vaccinia virus for use in a Phase 1b clinical trial to examine safety and efficacy in patients with renal cell carcinoma

April 2018

Application number:	APP203530
Purpose:	To import and release a genetically modified live-attenuated vaccinia virus for use in a Phase 1b clinical trial to examine safety and efficacy in patients with renal cell carcinoma.
Applicant:	SillaJen Biotherapeutics Inc
Application Lead:	Dr Tim Strabala

Executive summary and recommendation

On 4 April 2018, the EPA formally received an application from Clinical Network Services Pty Ltd to import and release a genetically modified live-attenuated vaccinia virus (Pexa-Vec; also known as JX-594) for use in a Phase 1b clinical trial to examine safety and efficacy in patients with renal cell carcinoma. The application was made on behalf of SillaJen Biotherapeutics Inc (the applicant), pursuant to section 34 of the Hazardous Substances and New Organisms Act 1996 (the HSNO Act).

Section 38I of the HSNO Act provides for a rapid assessment of applications received under section 34, if the applicant seeks the release of a qualifying organism. A qualifying organism is, a new organism (including a genetically modified organism) that is also a medicine or is contained in a medicine, as defined in section 3 of the Medicines Act 1981.

Based on the information in the application and other readily available sources, we found that it is highly improbable that the dose and route of administration of Pexa-Vec will have significant adverse effects on the health of the public or any valued species. Moreover, we found that it is highly improbable that Pexa-Vec could form a self-sustaining population and have significant adverse effects on the health of the public, any valued species, natural habitats, or the environment.

Therefore, we recommend that the application be approved, subject to the proposed controls.

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Purpose of this document

1. This Staff Assessment Report has been prepared by EPA staff to assist the decision-maker in considering application APP203530. It contains information from the applicant and other readily available sources, and it sets out the statutory criteria applicable to considering this application under the HSNO Act.

Application summary

2. On 20 December 2017, Clinical Network Services Pty Ltd lodged an application under section 34 of the HSNO Act (on behalf of SillaJen Biotherapeutics Inc; the applicant), which was formally received by the EPA on 4 April 2018 seeking approval to import and release a genetically modified live-attenuated vaccinia virus (Pexa-Vec; also known as JX-594). The applicant intends to use Pexa-Vec in a Phase 1b[1] clinical trial to examine safety and efficacy as a therapeutic oncolytic vaccine immunotherapy in patients with renal cell carcinoma (ie, a form of kidney cancer). The trial will also include treatment either with or without the monoclonal antibody REGN2810, developed by Regeneron Pharmaceuticals Inc, in a controlled study to determine Pexa-Vec's efficacy either with or without REGN2810 co-therapy. As REGN2810 is not an organism, and its formulation does not trigger any hazard classifications, it is not the subject of further consideration by EPA in its current formulation.

3. The applicant intends to conduct the Phase 1b clinical trial at various sites in New Zealand. The sites where Pexa-Vec will be used include public hospitals and associated facilities (such as pharmacies and laboratories) where Pexa-Vec will be transported, stored and prepared for intratumoural injection or intravenous introduction into patients with renal cell carcinoma. These sites will include laboratories where specimens from treated patients will be analysed to monitor patient safety during the clinical study. Private organisations (such as laboratories, courier companies and centralised vaccine storage and distribution centres) may also be contracted to provide services (per section 5 of the application).

4. Pexa-Vec treated patients will be allowed to return to their homes after Pexa-Vec is intratumourally administered.

The organism: Pexa-Vec

5. The organism Pexa-Vec (also known as Pexastimogene Devacirepvec, or JX-594) is a genetically modified live-attenuated vaccinia virus. The vaccinia virus strain from which Pexa-Vec is derived is a specific clone of the Wyeth strain (Nalca & Zumbrun 2010), which itself was selected in the Pexa-Vec manufacturing process from Dryvax™, a mixed population of Wyeth vaccinia strains (Anonymous 2014).

[1] A multiple dose escalation trial.

Vaccinia virus

6. The first medical application of vaccinia virus was as a vaccine against smallpox at some time before the 1930s (Fenner et al, 1988). Vaccination against smallpox using live vaccinia virus was effective because vaccination with vaccinia virus generates antibodies that cross-react with smallpox, providing protective immunity from it. The vaccinia virus vaccine was key to the Intensified Smallpox Eradication Programme established in 1966 by the World Health Assembly, which culminated in the global eradication of smallpox in 1980 (Fenner et al, 1988).

7. Four vaccinia strains, namely EM-63, Lister, New York City Board of Health (also known as the Wyeth strain), and Temple of Heaven were the strains most widely used in the many millions of vaccinations administered during the global smallpox eradication programme (Fenner et al, 1988).

8. Vaccinia virus has the following taxonomic classification by the International Committee on the Taxonomy of Viruses (ICTV):

   Family: Poxviridae (ie, viruses that cause “pockmarks” on the skin (Fenner et al, 1988));

   Subfamily: Chordopoxvirinae (ie, poxviruses that infect vertebrates);

   Genus: Orthopoxvirus;

   Species: Vaccinia virus

9. Vaccinia virus is an enveloped poxvirus that contains a linear double-stranded DNA genome. Upon infection of the host, the virus spreads through the blood, manifesting as leucocyte-associated viraemia[2] (Fenner et al, 1988; Chahroudi et al, 2005). From the blood, the virus spreads to epidermal tissues (Thorne et al, 2007) where it replicates in the cytoplasm of infected cells. Mature vaccinia virus particles (virions) are released when the infected epidermal cell (ie, skin and mucous membranes) undergoes virus-induced disintegration (lysis) (Fenner et al, 1988).

10. Following vaccination with vaccinia virus, a papule (a solid elevation of skin with no visible fluid, varying in diameter from 1 mm to 1 cm) typically develops within three to five days at the site of injection, which then becomes a pustule (a small bump on the skin that is filled with fluid or pus). A scab then forms, which eventually peels away leaving a pitted vaccination scar, typically by three weeks post-vaccination (Fenner et al, 1988; Lane & Fulginiti 2003). Vaccination produces a mild generalised infection in humans (swelling, tenderness of the draining lymph nodes), and viraemia is sometimes detectable between three to 10 days post-vaccination. Sometimes, vaccinia virus can be isolated from swabs of the respiratory tract following vaccination (saliva from swabbed tonsils, pharyngeal swabs etc.) (Fenner et al, 1988).

[2]Viraemia is the presence of viruses in the bloodstream.

11. Transmission of vaccinia virus from vaccinated individuals to unvaccinated individuals is rare (recorded as occurring 20-60 times for every million primary vaccinations administered in the 1950s and 1960s), and generally requires intimate physical contact (Lane & Fulginiti 2003).

12. Additional biological characteristics of vaccinia virus, and clinical observations following vaccination with vaccinia virus, are discussed where applicable in subsequent sections of this document.

The genetic modifications in Pexa-Vec

13. Pexa-Vec is a live-attenuated vaccinia virus modified with a single DNA insert that results in three differences relative to the wild-type Wyeth vaccine. The DNA insert contains two genes: one encoding human granulocyte macrophage-colony stimulating factor (hGM-CSF) and the other encoding a β-galactosidase enzyme (LacZ). The insertion disrupts the coding sequence for the native vaccinia virus thymidine kinase (an enzyme involved in DNA synthesis and required for vaccinia virus and Pexa-Vec replication) gene (Fig. 1).

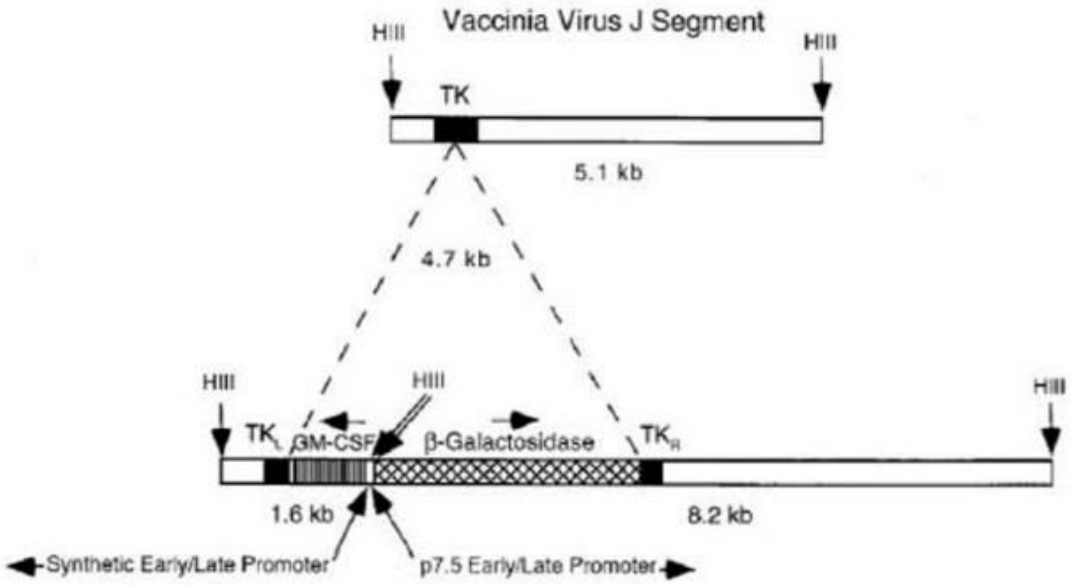

Figure 1. Schematic representation of the modifications contained in the Pexa-Vec genome. The Vaccinia virus J segment (HindIII restriction enzyme segment) is shown. The thymidine kinase (TK) gene is disrupted by a 4.7 kilobase pair insertion of a construct containing the human granulocyte-macrophage colony-stimulating factor (GM-CSF) gene, and a β-galactosidase gene, along with associated segments of DNA (Synthetic Early/Late Promoter and p7.5 Early/Late promoter and transcription termination sequences not shown in this diagram) involved in the regulation of expression of the two genes.

14. These modifications confer three specific properties on Pexa-Vec relative to vaccinia virus. First, deactivation of the viral thymidine kinase gene results in a diminished capability of Pexa-Vec to replicate within all but the most rapidly dividing cells (ie, cancer cells) because only these cells express sufficiently elevated levels of thymidine kinase to allow Pexa-Vec to replicate. This characteristic has been described in many peer-reviewed publications as ‘selective replication’ within cancer cells. Like vaccinia virus, Pexa-Vec causes replication-dependent cell lysis, which is the mechanism for its cancer cell-lysing (oncolytic) property. Second, expression of hGM-CSF stimulates systemic anti-tumour immunity in the patient (ie,

mechanism for the vaccine immunotherapy property). Third, the β-galactosidase enzyme provides a marker for viral replication in tumour biopsies, and in potential shedding or transfer of Pexa-Vec to caregivers (see section 3.1 of the application).

Intended use of Pexa-Vec

15. The applicant states that they intend to administer Pexa-Vec either intratumourally or intravenously in conjunction with the monoclonal antibody REGN2810 to patients with renal cell carcinoma (a form of kidney cancer) who are enrolled in a Phase 1b (multiple dose escalation) clinical trial.

16. Control 1 is proposed to limit the use of Pexa-Vec to intravenous and intratumoural administration of patients enrolled in a Phase 1b clinical trial (see paragraph 63). That means that Pexa-Vec cannot be used for any other purpose without a new HSNO Act approval.

17. In accordance with proposed Control 2 (see paragraph 63), EPA and MPI will be notified of the location of the clinical trial sites.

Potential benefits from Pexa-Vec use

18. There were 373 new registrations of kidney cancer in New Zealand in 2015[3], which makes it among the top 10 most prevalent cancers in the country (MoH 2017). The disease is approximately twice as prevalent among men as women (MoH 2017). Māori men have higher incidences of kidney cancer than non-Māori men, and Māori of both genders have higher incidences of mortality rates from kidney cancer than non-Māori (Robson et al, 2010, see application).

19. Data from previous clinical trials suggest that, in addition to its potential benefit for liver cancer (Liu et al, 2008; Park et al, 2008; Heo et al, 2011; Heo et al, 2013), Pexa-Vec also shows early promise as a candidate therapy for renal cell carcinoma (Kim et al, 2018). As such, the potential immediate benefits of Pexa-Vec to the patients recruited to the applicant's Phase 1b clinical trial include tumour shrinkage, alleviation of cancer symptoms and improved quality of life, cancer remission and prolonged survival (Kim et al, 2018, section 5 of the application).

20. Pexa-Vec also has the potential to benefit the wider New Zealand community with renal cell carcinoma, subject to positive results from the Phase 1b clinical trial described and regulatory approval for commercial release.

Potential adverse effects from Pexa-Vec use

21. Flu-like symptoms are common following Pexa-Vec treatment (Liu et al, 2008; Park et al, 2008; Breitbach et al, 2011; Heo et al, 2013; Kim et al, 2018). Other side effects experienced include: transient platelet deficiency in the blood, causing bruising and other symptoms (Park et al, 2008), nausea (Breitbach et al, 2011; Heo et al, 2013; Kim et al, 2018), fever, chills, vomiting,

[3] No specific data for renal cell carcinoma are available in Ministry of Health cancer statistics.

anorexia (Breitbach et al, 2011; Heo et al, 2013), rigors, low white blood cell count (Heo et al, 2013), anaemia (Kim et al, 2018), fatigue (Breitbach et al, 2011; Kim et al, 2018), headache, high and low blood pressure, rapid heart rate, and muscle pain (Breitbach et al, 2011).

Potential clinical complications of Pexa-Vec treatment based on the vaccination history of vaccinia virus

22. As described previously, vaccination with vaccinia virus usually produces a mild generalised infection in humans (swelling, tenderness of the draining lymph nodes) (see paragraph 10). However, vaccination with vaccinia virus is not without very low risk of the following significant clinical complications:

- **Eczema vaccinatum** is a severe, widespread infection of the skin that could occur in vaccinated or unvaccinated contacts who have eczema (frequency rate: 66 cases (no deaths) among approximately 14.1 million US vaccine recipients, and 60 contact-acquired cases (one death), for the year 1968 (Fenner et al, 1988));

- **Progressive vaccinia** is a severe, potentially fatal illness characterised by progressive necrosis at the site of vaccination that could occur in vaccinated individuals who suffer from a deficient immune system (frequency rate: 11 cases (four deaths) among approximately 14.1 million US vaccine recipients for the year 1968 (Fenner et al, 1988));

- **Generalised vaccinia** is characterised by a vesicular rash that sometimes covers the entire body. The rash is self-limiting and little or no therapy is administered (frequency rate: 141 cases (no deaths) among approximately 14.1 million US vaccine recipients, and two contact-acquired cases, for the year 1968 (Fenner et al, 1988));

- **Accidental infection** of a body part away from the inoculation site (eyelid etc.) is a common complication of vaccination with vaccinia virus (frequency rate: 149 cases (no deaths) among approximately 14.1 million US vaccine recipients, and 44 contact-acquired cases, for the year 1968 (Fenner et al, 1988));

- **Postvaccinial encephalitis** is a neurological complication of vaccination with vaccinia virus (frequency rate: 16 cases (four deaths) among approximately 14.1 million US vaccine recipients for the year 1968; (Fenner et al, 1988)).

23. The New York City Board of Health strain (also known as the Wyeth strain), which was one of the vaccines used during the smallpox eradication programme, had a somewhat lower pathogenicity, in terms of the frequency of clinical complications (Fenner et al, 1988).

24. Vaccinia virus is a Risk Group 2 microorganism[4], meaning it is unlikely to be a serious hazard to laboratory personnel, the community, animals, or the environment, and it presents a limited

[4]As Risk Group 2 is defined in the Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological aspects and containment facilities* (AS/NZS 2243.3.2002).

risk of infection spread. Further, there are effective treatments and preventive measures with respect to any infections that it may cause (outlined below; see paragraph 41).

25. There are no reports of Pexa-Vec inducing the aforementioned clinical complications, but they are still theoretical concerns regarding Pexa-Vec use. However, considering that Pexa-Vec is an attenuated strain of vaccinia virus, it is highly unlikely that the aforementioned clinical complications will develop following Pexa-Vec treatment.

Capacity of Pexa-Vec to replicate within cancer cells over normal cells

26. Vaccinia virus is known to exhibit an inherent tropism for tumour cells, replicating to higher levels in the tumour cell lines than in the normal cells (Thorne et al, 2007; Nalca & Zumbrun 2010; Heo et al, 2011). Additionally, rapidly proliferating cancer cells commonly express elevated levels of thymidine kinase (an enzyme involved in DNA synthesis and required for vaccinia virus and Pexa-Vec replication) but thymidine kinase levels are extremely low (almost undetectable) in resting/non-proliferating normal cells (Hengstschlager et al, 1994; Hengstschlager et al, 1998; Parato et al, 2012; Heo et al, 2014). As such, Pexa-Vec should selectively replicate within cancer cells (ie, high levels of cellular thymidine kinase) because Pexa-Vec contains a deactivated thymidine kinase gene.

27. In a clinical trial that involved intratumoural administration of Pexa-Vec to 14 liver cancer patients, tumour reduction was detected in some treated patients, and no healthy-organ toxicity was noted (Park et al, 2008). Although trials of Pexa-Vec to treat renal cell carcinoma are at an earlier stage, similar results are reported (Kim et al, 2018). The results in both of these reports support the hypothesis that Pexa-Vec replication is highly selective for cancer cells. Breitbach et al. (2011) have shown that Pexa-Vec selectively replicates within tumour tissue (colon, endometrial and rectal) over normal tissue *in vitro* (ie, most tumours had high-intensity staining for Pexa-Vec, whereas normal tissues did not (Breitbach et al, 2011)). Finally, Parato et al. (2012) have shown that while Pexa-Vec replicated in a variety of cancer cell types *in vitro*, eight normal tissues displayed either no apparent susceptibility to Pexa-Vec (normal tissue types: brain, lung, ovary, cervix, vulva, endometrium and kidney), or less sensitivity to Pexa-Vec infection (one of three normal colon/rectal cell samples).

28. Although gut crypt epithelial cells are highly proliferative, neither viral replication nor gut toxicity have been reported in normal colorectal tissue following Pexa-Vec treatment (Park et al, 2008; Breitbach et al, 2011).

29. Consistent with intratumoural replication and subsequent leakage into the systemic circulation through lysis of the cancer cells, Pexa-Vec has been detected in the blood of some treated patients up to five weeks post-administration in clinical trials (Park et al, 2008; Heo et al, 2013). However, although blood cells are highly proliferative, Breitbach et al. (2011) and Parato et al. (2012) have demonstrated *in vitro* that peripheral blood mononuclear cells (PBMCs) are highly resistant to Pexa-Vec replication.

30. Epidermal skin cells are rapidly proliferating cells, and as is to be expected, based on the biological properties of vaccinia virus (see paragraph 10), skin lesions have been reported following Pexa-Vec treatment (outlined in the following section of this document).

Capacity of Pexa-Vec to spread from treated patients

31. Some of the Pexa-Vec clinical trials have reported that one to two patients developed small skin pustules a few days after Pexa-Vec administration (approximately 5-10% of treated individuals; from one to 10 pustules per patient), but the pustules later cleared without complication (Breitbach et al, 2011; Heo et al, 2013).

32. A recent published study of more than 300 patients treated with Pexa-Vec (Breitbach et al, 2015) reported that 23% of patients (69/300) developed pustules following treatment, which resulted from 6% (72/1200) of all treatment administrations. To clarify, the patients were generally treated more than once, and the frequencies reported include both intravenous and intratumoural administration. The Pexa-Vec-induced pustules are similar in appearance and size (<10 mm in diameter) to pustules that were observed after administration of vaccinia virus in the smallpox vaccination campaign. However, the Pexa-Vec pustules generally tend to remain intact and be less prone to ulceration than vaccinia virus pustules. Further, all Pexa-Vec pustules have been self-limiting and cleared without complications or the need for specific anti-viral treatment, in trials to date (eg, Breitbach et al, 2015; Kung et al, 2015).

33. Of note, in all 14 patients treated only via intratumoural administration of Pexa-Vec, no throat swabs were found to be positive for Pexa-Vec (Park et al, 2008). However, viral shedding in throat swabs, rectal swabs and urine samples was observed in 35% of tested patients that were treated intravenously.

Capacity for Pexa-Vec to shed from treated patients to untreated individuals and induce significant adverse effects

34. Pexa-Vec transmission from treated individuals to untreated individuals has not been reported (see section 3.1 of the application), meaning Pexa-Vec transmission is currently only a theoretical concern based on the rare occurrence of vaccinia transmission from vaccinated individuals to close contacts (as discussed in paragraph 11).

35. A lack of evidence for Pexa-Vec transmission can likely be credited in part to the applicant instructing individuals before they receive treatment on how to avoid contact with pustules, should they form following treatment. This includes covering pustules with a non-occlusive dressing until a scab forms and peels away, laundering textiles and fabrics in hot water (71°C) with detergent and hot air drying, and instructing treated individuals not to touch their pustules or let anyone come into direct contact with them, as discussed in section 6.1 of the application, and Appendix C (SillaJen Pexa-Vec Guidelines) referenced therein.

36. Considering that vaccinia virus is completely inactivated within 60 minutes when treated at 55°C (within 90 minutes at 50 °C), and when it is exposed to sunlight (Fenner et al, 1988; Sagripanti et al, 2013), transmission of Pexa-Vec via contaminated surfaces is highly unlikely.

37. We note that Pexa-Vec treated individuals will be permitted to leave the clinical setting following Pexa-Vec administration, and may be required to cover pustules in non-clinical settings (their homes). Therefore, we propose Control 3 and Control 4.

38. Control 3 requires all individuals who are treated with Pexa-Vec be educated about the potential for Pexa-Vec transmission, and instructed on pustule management practices, before treatment (see paragraph 63).

39. Control 4 requires all individuals who are treated with Pexa-Vec to be provided with a biohazard container for disposal of used pustule dressings at home. These containers must be returned to the clinical trial site for medical waste disposal (see paragraph 63). This will provide for the appropriate disposal of dressings and other waste material that may carry Pexa-Vec.

40. In light of the aforementioned Pexa-Vec pustule management practices, and poor survival of the modified host when exposed to heat and sunlight, we consider that Pexa-Vec transmission from a treated individual to an untreated individual is highly unlikely. If transmission did occur, the level of exposure via pustules is predicted to be low compared to the doses received by Pexa-Vec treated individuals, and low compared to doses of vaccinia virus used in previous smallpox vaccination programmes (ie, the doses associated with the clinical complications described in paragraph 22). In the highly unlikely event of a Pexa-Vec infection resulting from the exposure of an untreated individual to a Pexa-Vec treated individual, the exposed individual would most likely clear attenuated Pexa-Vec via a normal immune response rather than experience a significant adverse reaction because Pexa-Vec replication is significantly impaired or non-existent in healthy tissue.

41. Therefore, we consider that the likelihood of an untreated individual being infected with attenuated Pexa-Vec and developing a significant adverse reaction is *highly improbable*. Regardless, if an untreated individual was to demonstrate virus-associated toxicity (confirmed by assaying for β-galactosidase; see paragraph 14), therapy could be initiated with vaccinia immunoglobulin (VIgG) and/or cidofovir (anti-viral agents shown to inhibit vaccinia virus replication (Thorne et al, 2007; Nalca & Zumbrun 2010)). A local stock of VIgG and cidofovir will be held in Singapore by the applicant and can be dispatched overnight to any New Zealand hospital if requested (see section 6.2 of the application).

Ability of Pexa-Vec to infect and replicate in animal hosts

42. In the unlikely event of Pexa-Vec transmission from a treated individual to a contacted animal, attenuated Pexa-Vec is not expected to replicate within the healthy tissue of the animal because Pexa-Vec replication exhibits selectivity for tumours. Kim et al. (2006) have demonstrated Pexa-Vec tumour selectivity in a rabbit animal model with minimal or no virus detected in the normal tissues (including lung, liver, ovary, kidney, spleen, heart, skeletal muscle, bone marrow and colon tissue) (Kim et al, 2006).

43. EPA staff did not identify any pre-clinical Pexa-Vec studies that involved avian species. Of note, no reports of vaccinia virus ever infecting birds during its long use as a vaccine were identified either.

44. Therefore, we consider that the likelihood of untreated animal species being infected with attenuated Pexa-Vec and developing a significant adverse reaction is *highly improbable*.

Genetic stability of Pexa-Vec and capacity to recombine with other poxviruses

45. Double-stranded DNA viruses, such as vaccinia virus, typically have very low rates of mutation from one cellular passage to the next (Nalca & Zumbrun 2010).

46. Pexa-Vec could revert its genome back to that of the unmodified vaccinia virus (ie, the Wyeth vaccinia strain) by eliminating the genes inserted in the thymidine kinase gene (ie, genes for hGM-CSF and LacZ, and regulatory elements). However, genetic stability studies of Pexa-Vec have not detected spontaneous revertants (section 3.1 of the application).

Recombination in orthopoxviruses

47. Horizontal gene transfer (HGT) is the stable transfer of genetic material from one organism to another without reproduction or human intervention. For viruses, HGT can occur via genetic recombination between replicating viruses within a co-infected cell (Keese 2008) – such events have the potential to generate a novel virus with altered pathogenic properties.

48. Genetic recombination between vaccinia virus strains *in vitro* has been reported (Fenner & Comben 1958; Yao & Evans 2003). Genetic recombination has also been reported to occur between other species of orthopoxviruses *in vitro*, within laboratory animals and in nature (Gershon et al, 1989). However, EPA staff did not identify any reports of recombination among vaccinia strains, other orthopoxviruses, or the closely related parapoxviruses, which infect sheep, goats, cattle, and deer in New Zealand (McFadden & Rawdon 2012), under natural conditions.

49. The likelihood that administered Pexa-Vec (or shed Pexa-Vec) will recombine with other poxviruses within treated individuals (or within infected untreated individuals or animals) and yield recombinant poxviruses of concern (ie, an undesirable self-sustaining population), is unlikely given that:
    - In the long history of mass vaccination against smallpox using vaccinia virus, there is not one reported instance of a transmissible vaccinia strain taking hold and spreading through a vaccinated region (within people or animals);
    - If a Pexa-Vec viral recombinant was generated within a treated individual, the recombined virus would likely remain within the individual, because Pexa-Vec transmission from a treated individual has never been reported (Pexa-Vec is only a theoretical concern based on the vaccination history of the unmodified host);
    - If an untreated individual or animal infected with a poxvirus were exposed and subsequently infected with Pexa-Vec, genetic recombination could only occur in the short period where

any poxviruses were viraemic (see paragraph 10), or when the replicating poxviruses co-infect a cancerous cell (Pexa-Vec replication is highly impaired or non-existent in normal cells).

50. Therefore, we consider the likelihood of a virulent recombinant Pexa-Vec virus forming is *highly improbable*.

Information from other agencies

51. The Department of Conservation (DOC), the Ministry for Primary Industries (MPI) and the Ministry of Health (MoH) were given the opportunity to comment on the application.

52. DOC noted that the application does not appear to have any biodiversity implications, and that they had no further comments on the application. MPI and MoH did not comment on the application.

Legislative criteria to be considered

53. Section 38I of the HSNO Act provides for the rapid assessment of applications that seek to release qualifying organisms. A qualifying organism is, in part, a new organism that is or is contained in a medicine (as defined in section 3 of the Medicines Act 1981).

54. Pexa-Vec is a medicine as it is (a) supplied for administering to 1 or more human beings for a therapeutic purpose; and (b) it achieves, or is likely to achieve, its principal intended action in the human body by immunological and metabolic means (in accordance with section 3 of the Medicines Act 1981).

55. In order to be approved for release as a qualifying organism, section 38I(3) of the HSNO Act requires that the decision-maker be satisfied that, taking into account all the controls that will be imposed (if any), it is highly improbable that:

(a) the dose and routes of administration of the medicine would have significant adverse effects on-

(i) the health of the public; or

(ii) any valued species; and

(b) the qualifying organism could form an undesirable self-sustaining population and would have significant adverse effects on-

(i) the health and safety of the public; or

(ii) any valued species; or

(iii) natural habitats; or

(iv) the environment.

56. In doing so, the effects of the medicine or qualifying organism in the person who is being treated with the medicine are not to be taken into account as per section 38I(4) of the HSNO Act.

57. In the first instance, we have assessed the organism against these criteria. This assessment is set out in the following section of this report.

58. If the organism is not approved under this section, the EPA must assess and determine this application under section 38, as per section 38I(2) of the HSNO Act.

Assessment of the risk of Pexa-Vec conditional release against legislative criteria

59. It is highly improbable that the dose and intratumoural administration of Pexa-Vec to individuals with renal cell carcinoma will have significant adverse effects on the health of the public or any valued species, given that:
    - Pexa-Vec transmission from treated individuals to untreated individuals/animals has not been reported, and transmission of unmodified strains of vaccinia virus from vaccinated individuals to unvaccinated individuals/animals is rare;
    - In the highly unlikely event of a Pexa-Vec infection resulting from the exposure of an untreated individual/animal to a Pexa-Vec treated individual, an exposed individual/animal would most likely clear attenuated Pexa-Vec rather than experience an adverse reaction because Pexa-Vec replication is significantly impaired or non-existent in healthy tissue.

60. Moreover, it is highly improbable that Pexa-Vec could form an undesirable self-sustaining population that would have significant adverse effects on the health and safety of the public, any valued species, natural habitats or the environment, given that:
    - Pexa-Vec replication is significantly impaired or non-existent (attenuated) in healthy tissue due to deactivation of the thymidine kinase gene;
    - Pexa-Vec attenuation is genetically stable;
    - Formation of a self-sustaining Pexa-Vec/poxvirus recombinant is highly unlikely because genetic recombination could only occur in the short period where the poxviruses were viraemic, or if the replicating poxviruses co-infected a cancerous cell.

Conclusion and recommendation

61. Based on the intrinsic properties of vaccinia virus and the specific properties of attenuated Pexa-Vec, we consider that it is highly improbable that Pexa-Vec will have any significant adverse effects on the health and safety of the public, any valued species, natural habitats or the environment if Pexa-Vec is used in a Phase 1b clinical trial for patients with renal cell carcinoma.

62. We acknowledge that all clinical trials in New Zealand are expected to be conducted in accordance with the standards set out in the *Note for Guidance on Good Clinical Practice* (Medsafe 2015); and that all New Zealand clinics and hospitals are expected to follow New

Zealand *Health and Disability Services (Infection Prevention and Control) Standards* (NZS 8134.3.3:2008)[5].

63. We recommend that this application to import and release Pexa-Vec (JX-594) be approved subject to the following controls:

Control 1 - The organism (Pexa-Vec; JX-594) must only be intravenously or intratumourally administered to individuals with renal cell carcinoma who are enrolled in a Phase 1b clinical trial to examine the safety and efficacy of Pexa-Vec in patients with renal cell carcinoma.

Control 2 - The EPA and MPI must be notified, in writing, of the location of any clinical trial site before this approval is used at the site for the first time.

Control 3 - Individuals who are treated with the organism must be educated about the potential for Pexa-Vec transmission to untreated individuals and animals, and instructed on pustule management practices, before treatment.

Control 4 - Individuals who are treated with the organism must be provided with a biohazard container for disposal of used pustule dressings when away from the clinical trial site. These containers must be returned to the clinical trial site for disposal as medical waste.

Control 5 - Any occurrence of Pexa-Vec-induced adverse effects resulting from Pexa-Vec transmission from Pexa-Vec treated individuals to untreated individuals or animals must be reported to the EPA and MPI as soon as possible. In the event of such an occurrence, the EPA may consider reassessing the approval.

Control 6 – The New Zealand sponsor must ensure adequate stocks of Vaccinia immunoglobulin and cidofovir are stored by at least one Phase 1b clinical trial site for the duration of the trial.

Control 7 – A report that shows compliance with the above controls must be submitted to the EPA and MPI on or before 30 June every year from the commencement of the clinical trial to the conclusion of the clinical trial.

64. The EPA, Clinical Network Services Pty Ltd, and SillaJen Biotherapeutics Inc recognise that an approval granted under section 38I of the HSNO Act is not an approval to use a qualifying medicine until the medicine has been approved for use under the Medicines Act 1981.

[5]General practices are expected to operate in accordance with Australian/New Zealand Standard (AS/NZS): Office-based health care facilities - Reprocessing of reusable medical and surgical instruments and equipment, and maintenance of the associated environment (AS/NZS 4815:2006).

Laboratories are expected to adhere to various standards, including AS/NZS 2243.3:2002: Safety in laboratories - Microbiology safety and containment.

References

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