Environmental Protection Authority
Te Mana Rauhī Taiao

New Zealand Government

Decision

Date	16 April 2019
Application number	APP202371
Application type	To import for release or release from containment a qualifying organism under section 38I of the Hazardous Substances and New Organisms Act 1996
Applicant	Sanofi-Aventis New Zealand Limited
Date Application received	3 April 2019
Considered by	The Chief Executive of the Environmental Protection Authority[1]
Purpose of the application	To import for release a genetically modified live-attenuated chimaeric flavivirus vaccine (IMOJEV®) to protect humans against Japanese encephalitis.
The new organism approved	IMOJEV® (Chimerivax™-JE, as described in Table 1)

Summary of the decision

1.1 Application APP202371, to import for release a genetically modified live-attenuated chimaeric flavivirus vaccine (IMOJEV®) for marketing and distribution to health care providers for the immunisation of travellers to regions where Japanese encephalitis virus is endemic, was lodged under section 34 of the Hazardous Substances and New Organisms Act 1996 (the Act).

1.2 I considered the application in accordance with the relevant provisions of the Act and of the Hazardous Substances and New Organisms (Methodology) Order 1998 (the Methodology).

1.3 I approve the application in accordance with section 38I of the Act.

[1] The Chief Executive of the EPA has made the decision on this application under delegated authority in accordance with the delegation dated 6 May 2016 from the EPA to the Chief Executive pursuant to section 19 of the Act.

2 Application and consideration process

Application receipt

2.1 Application APP202371 was formally received by the Environmental Protection Authority (EPA) for consideration on 3 April 2019.

Purpose of the application

2.2 The applicant, Sanofi-Aventis New Zealand Limited, applied to the EPA to import for release a genetically modified chimaeric live-attenuated Japanese encephalitis virus vaccine (IMOJEV; also known as Chimerivax-JE). The applicant intends to market and distribute IMOJEV to healthcare providers for the vaccination of travellers to east, southeast, and south Asia, regions where Japanese encephalitis is an endemic disease. In addition to tourists to the region, the vaccine is expected to benefit military personnel and workers dispatched on aid missions to these regions, by protecting them from the virus, with a shorter time to acquire immunity than other approved Japanese encephalitis virus vaccines.

The organism

2.3 I am advised that IMOJEV was created by utilising the common genomic structures of flaviviruses to substitute the pre-membrane (prM) and envelope protein (E) genes from the live-attenuated Japanese encephalitis virus vaccine strain SA14-14-2 for those of the live-attenuated Yellow fever virus vaccine strain YF17D-204. The resulting chimaeric live-attenuated virus vaccine features the E protein (supported by the underlying mature membrane (M) protein) on its surface, which elicits a protective immune response in the vaccine recipient. I am further advised that the recombinant viral vaccine contains the gene encoding the non-surface core (C) protein and the non-structural genes (NS1-NS5) from YF17D-204. The vaccine is dependent on these YF17D-204 NS genes for its replication and associated functions.

2.4 According to the EPA staff report, when IMOJEV is administered as a single dose to a recipient, the virus undergoes limited replication in the recipient, and an immune response is rapidly elicited, which provides protective immunity in 93% of vaccine recipients within 14 days, and 99% of vaccine recipients within 30 days. The vaccine thus provides rapid and long-lasting immunity to recipients, estimated to be approximately 20 years.

Decision pathway assessment

2.5 Section 38I of the HSNO Act provides for a rapid assessment of applications received under section 34, if the application seeks the release of a qualifying organism. A qualifying organism is, in part, a new organism that is a medicine or is contained in a medicine. Additionally, any qualifying organism must meet the requirements of section 38I(3) of the Act.

2.6 IMOJEV meets the definition of a medicine as defined in section 3 of the Medicines Act 1981, as it is a substance or article that—

(i) is manufactured, imported, sold, or supplied wholly or principally for administering to 1 or more human beings for a therapeutic purpose; and

(ii) achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, or metabolic means.

2.7 IMOJEV meets the definition of a new organism because it is a genetically modified organism in accordance with section 2A(1)(d) of the Act; and

2.8 According to the preliminary risk assessment provided in the IMOJEV pathway assessment advice, IMOJEV was likely to meet the criteria set out in section 38I(3) of the Act, because it is highly improbable that—

(a) the dose and routes of administration of the medicine or veterinary 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.

2.9 The criteria of section 38I(3) of the Act as applied to IMOJEV are further described in section 3 of this decision document.

2.10 The staff decision pathway assessment noted that IMOJEV could also be assessed under section 38 of the Act. However, I deemed section 38I to be the appropriate assessment pathway because the section 38I pathway is intended specifically for medicines. Furthermore, its approval for release by EPA would not make IMOJEV an unregulated organism, since it would still be regulated under the Medicines Act. I was advised that public interest in previous release approvals for GMO medicines have generated only low levels of public interest, and therefore I deemed that full public notification of the application was not necessary.

2.11 Therefore, I decided that the most appropriate and effective means of assessing IMOJEV was by the pathway directed by section 38I of the Act.

Comments from Medsafe, DOC, and MPI

2.12 In accordance with section 58(1)(a) of the Act, the Department of Conservation (DOC), the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), and the Ministry for Primary Industries (MPI) were provided with the application and asked for comment.

2.13 Medsafe stated that they had “no concerns” with the application, and that it was highly likely that IMOJEV would be regulated by Medsafe as a prescription-only medicine for administration by trained medical practitioners.

2.14 DOC stated that they had no objections to the application.

2.15 MPI stated that the importation of IMOJEV is not foreseen to be an issue, noting the attenuated nature of both the vaccine and its parental vaccine strains. The MPI comments noted the low titres and short duration of viraemia in humans. They also questioned how the tracking of disposal of IMOJEV would occur.

2.16 MPI further commented that, assuming approval of this application from EPA, a Chief Technical Officer (CTO) direction would be required to allow the importation of IMOJEV under a general import permit, because the Microorganisms Import Health Standard (MICROIC.ALL) requires new organisms to be directed to a containment facility.

2.17 I note that MPI’s comments are predicated on the assumption that IMOJEV would be approved as a new organism for release with controls. However, I further note that granting an approval to release IMOJEV as a qualifying organism without controls under section 38I of the Act means that it is no longer a new organism, per section 2A(2)(b)(ii) of the Act.

2.18 Regardless of this point, I acknowledge that IMOJEV requires appropriate disposal. However, I am advised that there is a high improbability that IMOJEV will have adverse effects on the health of the public or any valued species, and a high improbability that IMOJEV could form an undesirable self-sustaining population (as detailed in the EPA Staff Assessment Report, and section 3 of this document). Therefore, I consider that there is no need to track the disposal of IMOJEV beyond what may be required under the Medicines Act 1981, and/or the Ministry of Health’s *Immunisation Handbook.*

Information available for the consideration

2.19 The information available for my consideration comprised:

- the application and references provided therein;
- the EPA Staff Assessment Report;
- two letters solicited by the applicant from travel medicine specialists in support of the application; and
- comments received from Medsafe, DOC, and MPI.

2.20 I had sufficient information to assess the application. To the extent that the application may not meet any legislative information requirements, I waive those requirements.

Legislative matters considered

2.21 I considered the application in accordance with section 38I of the Act[2], taking into account the relevant matters in Part 2 of the Act, and the Methodology.

3 Assessment of IMOJEV against legislative criteria

3.1 I note from the application that the applicant intends to market and distribute IMOJEV to trained medical practitioners for use as a prescription-only medicine for the vaccination of people who plan to travel to regions where Japanese encephalitis virus is endemic. Because (a) it is 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, I am satisfied that IMOJEV is a medicine (as defined in section 3 of the Medicines Act 1981).

3.2 I have made a rapid assessment of the adverse effects of importing IMOJEV under section 38I of the Act. Specifically, and in accordance with section 38I(3), I considered the capacity of IMOJEV to have significant adverse effects on:

- the health of the public or any valued species through inadvertent transmission of IMOJEV; and
- the health and safety of the public, any valued species, natural habitats or the environment through recombination or spontaneous mutation resulting in the formation of an undesirable self-sustaining population.
- the health and safety of the public, any valued species, natural habitats or the environment via improper handling or disposal of the vaccine resulting in the establishment of an undesirable self-sustaining population

3.3 In considering the potential significant adverse effects of IMOJEV, I did not take into account any effects of the medicine on the individual that is to be treated with the medicine, in accordance with section 38I(4) of the Act.

Potential for significant adverse effects through inadvertent transmission

3.4 I note that IMOJEV replication is significantly impaired relative to the wild-type viruses from which it is derived. I note that this impaired replication means that the levels of IMOJEV viraemia are too low to allow any shedding of the vaccine by the recipient.

3.5 Regardless of this point, I am advised that it is theoretically possible that IMOJEV might be transmitted to another person via a blood donation while the vaccine recipient is still viraemic. However, the staff advice further notes that this theoretical possibility is true of any of the live-attenuated virus vaccines that are used in New Zealand, and the New Zealand Blood Service

[2] As detailed in section 3 of this document.

screens out any potential blood donors who have received any live-attenuated virus vaccine for a period of four weeks after vaccination.

3.6 Additionally, I note from the staff advice that it is theoretically possible that IMOJEV might be transmitted to the foetus of a woman who receives IMOJEV during pregnancy. However, the staff advice notes that guidelines for medical practitioners in the Ministry of Health's *Immunisation Handbook* recommend advising women of child-bearing age that they should not become pregnant within 4 weeks of receiving any live-attenuated viral vaccine. The staff advice also notes that the *Immunisation Handbook* also advises medical practitioners that "live vaccines should be avoided until after the delivery". The *Immunisation Handbook* goes on to state that this recommendation is purely a precautionary measure, noting that examination of children born to pregnant women who inadvertently received live-attenuated vaccines showed no adverse effects. I am further advised that animal studies conducted by the applicant demonstrated no adverse effects in rabbit kittens born to does that had received IMOJEV.

3.7 I note that, because of the poor survival of IMOJEV virus when it is exposed to heat, sunlight, desiccation, disinfectants or detergents, the staff advice considered that the transmission of IMOJEV from a treated person to an untreated person or animal by any other means is highly improbable. If transmission did occur, the level of exposure is predicted to be low, relative to the doses that will be received by IMOJEV-vaccinated persons.

3.8 Furthermore, I note from the staff advice that in the 80-year history of vaccination against yellow fever, there were no reports of the YF17D-204 Yellow fever virus vaccine strain being spontaneously transmitted (ie, not via human administration) either among people or animals. Similarly, there are no known instances of IMOJEV being spontaneously transmitted since it was first approved for use in humans in 2010.

3.9 I am advised that in the highly unlikely event of an IMOJEV infection resulting from the exposure of an untreated person or animal to an IMOJEV treated individual, IMOJEV will only replicate poorly in humans, and it will not replicate at all in normal Japanese encephalitis virus hosts (eg, pigs and mosquitoes). I note that it was further considered in the staff advice that the natural immune response of any exposed person or animal would likely quickly eliminate any IMOJEV. I note that such immune responses are the basis for the use of IMOJEV as a vaccine.

3.10 Therefore, I am satisfied that, in the highly improbable event that IMOJEV is inadvertently transmitted to an unintended person or animal, it is highly improbable that IMOJEV will have significant adverse effects on the health of the public or any valued species.

Potential for significant adverse effects through recombination or spontaneous mutation resulting in the establishment of an undesirable self-sustaining population

3.11 I note that the staff advice considered that it is theoretically possible that IMOJEV could revert to a virulent form via spontaneous mutation of the vaccine. However, I am advised that for

virulence to be restored, six independent mutations would be required in the vaccinated person. I am further advised that such a sequence of events is highly improbable, because IMOJEV is known to be highly genetically stable, as are both of the vaccines from which it is derived.

3.12 I considered the likelihood that administered IMOJEV might potentially recombine with other flaviviruses and form an undesirable self-sustaining population. I note from the staff advice that the formation of such a recombination event is highly unlikely, considering that flaviviruses undergo recombination extremely rarely, and that such genetic recombination could only occur within vaccinated individuals who are infected with another flavivirus in the short period where the viruses are viraemic.

Potential for significant adverse effects through improper handling or disposal of the vaccine resulting in the establishment of an undesirable self-sustaining population

3.13 I considered the possibility that IMOJEV might be spread through improper handling or disposal of the vaccine. I note from the staff advice and the comments from Medsafe that IMOJEV will only be used by trained medical practitioners who understand the proper handling and disposal of any live-attenuated vaccine. Further, I note that the staff advice considered that the likelihood of a self-sustaining population establishing from either of these routes is highly improbable given the instability of the vaccine outside a host and its effects on potential hosts, as described above.

3.14 Therefore, I am satisfied that it is highly improbable that IMOJEV will 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.

Achieving the purpose of the Act

3.15 The purpose of the Act is to protect the environment, and the health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms (section 4 of the Act).

3.16 In order to achieve the purpose of the Act, when considering the application I recognised and provided (to the extent necessary) for the following principles (section 5) of the Act:

- the safeguarding of the life-supporting capacity of air, water, soil and ecosystems; and
- the maintenance and enhancement of the capacity of people and communities to provide for their own economic, social and cultural well-being and for the reasonably foreseeable needs of future generations.

3.17 I took into account the following matters when considering the application in order to achieve the purpose of the Act (sections 6, 7 and 8 of the Act):

1. the sustainability of all native and valued introduced flora and fauna;
2. the intrinsic value of ecosystems;

3. public health;
4. the economic and related benefits and costs of using a particular new organism;
5. the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects;
6. New Zealand's international obligations;
7. the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, wāhi tapu, valued flora and fauna, and other taonga; and
8. the principles of the Treaty of Waitangi (Te Tiriti o Waitangi).

3.18 I consider that matters 1-5 have been taken into account as matters for consideration under section 38I of the Act.

3.19 I note from the staff advice that New Zealand's international obligation pertaining to this decision, as a Party to the Cartagena Protocol on Biosafety, is the requirement to report the decision to the United Nations Biosafety Clearing House.

3.20 I took into account the possible effects on the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, wāhi tapu, valued flora and fauna, and other taonga, and the principles of the Treaty of Waitangi (Te Tiriti o Waitangi), as advised by a cultural risk assessment from the EPA's Māori advisory unit, Kaupapa Kura Taiao within the staff advice. These matters are addressed in detail under the following subheading.

Potential for significant adverse effects on Māori culture, traditions, and Te Tiriti o Waitangi

3.21 I note that the cultural risk assessment considered that IMOJEV would protect the taha hauora (human health and well-being of Māori and other New Zealanders, through protection of taha tinana (physical health and well-being) and taha wairua (spiritual health and well-being), as well as taha whanaunga (caring for, and sharing in the collective, including relationships and whanau).

3.22 I note that the risk assessment went on to state that the release of IMOJEV is not likely to adversely affect Māori interests, including Māori communities, culturally significant species and materials, nor any associated cultural values and practices.

3.23 I note that the assessment considered that immunisation with IMOJEV is voluntary, and that there are alternative vaccines available, thus respecting the mana of individuals.

3.24 Finally, I note that the Kaupapa Kura Taiao assessment considered that benefits would accrue to Māori by:

- Enhancing *oranga pai me te toiora* - quality of life and enjoyment of healthy life styles.
- Enhancing *mauri* (vital essence) and *manawaroa* (resilience) of individuals.
- Preventing *hauātanga* - impairment of functions and potential to participate fully at work, play, home or in society.
- Protecting against *ngā whakakino i ngā pūnaha ā tinana* - adverse effects on body organs and/or systems.

3.25 After assessing all the information, I did not identify any adverse effects on the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, wāhi tapu, valued flora and fauna, and other taonga.

3.26 I am satisfied that this decision is consistent with and achieves the purpose of the Act and the above principles and matters.

4 Associated approvals

4.1 I note that the applicant intends to submit IMOJEV to Medsafe for approval as a medicine under the Medicines Act 1981. However, section 29 of the Medicines Act allows the use of a medicine prior to its registration by Medsafe. Such use is allowed only at the request of a medical practitioner for the treatment of a particular patient. Any medical practitioner so using IMOJEV would be required to report the sale and supply of the medicine to the Director-General of the Ministry of Health, identifying the medical practitioner, the patient, as well as when and where the medicine was sold or supplied. These requirements mean that IMOJEV would be treated in effectively the same way as a registered prescription medicine, with an additional requirement of reporting its sale and use to the Ministry of Health.

4.2 Regardless of these points, I note that this approval cannot be used until any requirements under the Biosecurity Act 1993 have also been met.

5 Decision

5.1 After reviewing all of the information contained in the application, the EPA Staff Assessment Report, two letters from travel medicine specialists in support of the application, as well as comments received from Medsafe and DOC, I am satisfied that the application meets the requirements of section 38I of the Act.

5.2 I am satisfied, and therefore determine, that IMOJEV is a qualifying medicine, and thus a qualifying organism, as defined in section 2(1) of the Act for the following reasons:

- IMOJEV meets the definition of a medicine as defined in section 3 of the Medicines Act 1981;
- IMOJEV is a new organism in accordance with section 2A(1)(d) of the Act; and
- IMOJEV meets the criteria set out in section 38I(3) of the Act.

5.3 I **approve** the importation for release of IMOJEV **without controls** under section 38I of the Act.

5.4 I note that, in accordance with section 2A(2)(b)(ii) of the Act, as a result of this decision, IMOJEV is not a new organism under the Act.

16 April 2019

Dr Allan Freeth **Chief Executive** **Environmental Protection Authority**	

Organism	Approval code
IMOJEV® (Chimerivax™-JE) IMOJEV is a chimaeric Yellow fever/Japanese live-attenuated virus strain that contains the non-structural protein genes from Yellow fever live-attenuated vaccine strain YF17D-204, and the pre-membrane (prM) and envelope (E) genes from Japanese encephalitis live-attenuated vaccine strain SA14-14-2.	GMR100006