Summary Report of Risk Assessment Conducted Pursuant to subsection 108(1) of the *Canadian Environmental Protection Act, 1999*

New Substances Notification 21343: Recombinant Human T-cells transduced with a non-replicative lentiviral vector expressing a chimeric antigen receptor binding the human B-cell cell surface proteins CD19 and CD22 (IMJ995)

Regulatory decision

Under the provisions for Animate Products of Biotechnology in Part 6 of the *Canadian Environmental Protection Act, 1999* (CEPA), and pursuant to section 108 of the Act, the Minister of the Environment and the Minister of Health have assessed information in respect of the substance, IMJ995, that is a living organism. It was determined that IMJ995 is not suspected or anticipated to enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long term harmful effect on the environment or its biological diversity, constitute or may constitute a danger to the environment on which life depends, or constitute or may constitute a danger to human life or health in Canada. Therefore, no further action is recommended as a result of this assessment.

Identity, notified and potential uses

The notified organism (IMJ995) is a population of human white blood cells (T cells), that are genetically modified using a replication incompetent and self-inactivating lentiviral vector (LVV). As such, these cells can express genetically modified receptors that target specific surface proteins expressed by a "malignant subset" of a different group of white blood cell (B cells). Upon administration, IMJ995 will specifically target and destroy the malignant B cells in patients with relapsed or refractory acute lymphoblastic leukemia (r/r ALL).

IMJ995, was notified for its import for use as an investigational immunotherapy product for use in children and adult patients with r/r ALL. Other potential use could include its use as a commercial immunotherapy therapy product.

Exposure assessment

<u>The environmental exposure potential of IMJ995 is assessed to be low because:</u>

1. In the unlikely event that IMJ995 is released to the general environment, it is not expected to survive as human T cells cannot survive outside of the human body. In addition, the genetic modifications are not expected to provide a selective survival advantage over wild-type human T cells. Taken together, exposure to the general population and the environment is unlikely.

2. In addition to the planned importation for the intended use, IMJ995 could potentially be used as a commercial immunotherapy product or manufactured in Canada. Regardless of the type of use,

IMJ995 is not expected to remain viable in the environment outside of the body of the treated patients and not expected to significantly increase exposure to the environment particularly with quality control measures and biosafety procedures in place. Taken together, exposure to the environment is unlikely.

The indirect human exposure potential of IMJ995 is assessed to be low because:

1. If the proposed clinical trial is initiated, the target dose of IMJ995 cells would be imported into Canada during the course of the clinical trial to treat a maximum of three patients under controlled conditions in a clinical site by properly trained health care professionals.

The following were also taken into account in the human health and environmental exposure considerations for IMJ995:

1. The notifier does not intend to manufacture IMJ995 in Canada. Should it be manufactured in Canada, the environmental exposure would not be expected to significantly increase, as manufacturing processes, quality control measures and biosafety procedures in place to prevent the release into the environment.
2. General bio-safety measures in healthcare settings and contingency plans for accidental spills are expected to be in place.
3. The LVV present in IMJ995 is unlikely to be shed from treated patients due to genetic modifications that have rendered it replication-incompetent and self-inactivating.

Hazard assessment

The environmental hazard potential of IMJ995 is assessed to be low because:

1. Similar to wild-type human T cells, IMJ995 requires the specific physiological conditions of the human body to survive. As such, the IMJ995 cells are not capable of persisting or proliferating in aquatic or terrestrial plants, invertebrates, or non-human vertebrates.

The human health hazard potential of IMJ995 is assessed to be low because:

1. The likelihood of mobilization and recombination of the integrated lentiviral gene sequences to become a functional transmissible virus due to pre-existing infections with other viruses of close lineage is extremely low, as several unlikely events would be required for the LVV to obtain the genes for replication or virulence.
2. Available results from ongoing and completed clinical studies outside Canada investigating effects of surrogate organisms (i.e. genetically modified human T cells carrying the same LVV that expresses a different chimeric antigen receptor) indicated that treatment with IMJ995 could potentially cause predictable and clinically manageable adverse events. However, those events have been mainly

resolved with clinically manageable measures[1] and will not be expected in members of the general population.

Hazards related to micro-organisms used in the workplace should be classified accordingly under the Workplace Hazardous Materials Information System (WHMIS)[2].

The following were also taken into account in the human health and environmental hazard potential for IMJ995:

1. The genetic modifications in IMJ995 are well defined and stably integrated. The LVV contains synthetic genes of human origin, and they are not known to have any pathogenic, oncogenic, or toxic properties in human and non-human species.
2. The LVV used to transduce the human T cells is replication-incompetent and self-inactivating. It does not contain any antimicrobial resistance genes, virulence genes or genes of unknown function(s). As a result, it is not expected to cause any adverse effects in humans or in the environment.
3. The results of the pre-clinical studies in rodents to determine the effects of IMJ995 did not result in any observable adverse effects, toxicity or mortality at any dose tested.

Risk characterization

Risk is typically described as the probability of an adverse effect occurring based on hazards and a particular scenario of exposure. In the present case, the organism will be imported and used as an investigational gene therapy product for treatment of r/r ALL. Owing to the low potential hazard and the low potential exposure, the environmental and human health risks associated with the use of IMJ995 as an investigational or commercial immunotherapy product for use in adult and paediatric patients with r/r ALL is assessed to be low.

The assumptions made in the assessment are considered to be adequately protective for the general population as well as for subpopulations who may be more susceptible or highly exposed.

Risk assessment conclusion

There is no evidence to suggest a potential risk of adverse environmental effects at the exposure levels predicted for the Canadian environment from the use of IMJ995 as an investigational or commercial immunotherapy product in adult and paediatric patients with r/r ALL. The risk to the environment

[1] In Canada, biologic drugs are assessed for safety, quality and efficacy under the *Food and Drugs Act* and Regulations, administered by the Biologic and Radiopharmaceutical Drugs Directorate of Health Canada.

[2] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposure in the general environment. For humans, this includes, but is not limited to, exposure from air, water and the use of products containing the substances. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the criteria in the *Hazardous Products Regulations,* which is part of the regulatory framework for the Workplace Hazardous Materials Information System (WHMIS) for products intended for workplace use.

associated with IMJ995 is not suspected to meet the criteria in paragraphs 64(a) or (b) of CEPA. No further action is recommended.

Similarly, there is no evidence to suggest a risk of adverse human health effects at the exposure levels predicted for the general Canadian population from the use of IMJ995 as an investigational or commercial immunotherapy product in adult and paediatric patients with r/r ALL. The risk to human health associated with IMJ995 is not suspected to meet the criteria in paragraph 64(c) of CEPA. No further action is recommended.