Risk assessment summary

for

NSN 19445: Ad26.Mos1.Env.

(For use as part of an investigational vaccine for prevention and treatment of HIV-1 infection)

Introduction

Under the *Canadian Environmental Protection Act,* 1999 (CEPA), animate products of biotechnology (i.e. “living organisms”) not listed on the Domestic Substances List (DSL) are considered “new” to Canada. Information and data prescribed by the *New Substances Notification Regulations (Organisms*) [NSNR(O)] in regards to the new organism must be submitted before that new organism is manufactured or imported in Canada. Environment and Climate Change Canada (ECCC) and Health Canada (HC) must assess that information and data to determine if the new organism has potential to harm human health and the environment. Under these Regulations, ‘harm to human health’ is assessed as the potential to cause harm to humans thorough an environmental exposure (the efficacy of the substance as well as its safety through the direct exposure to patients are assessed under the *Food and Drugs Act*).

Ad26.Mos1.Env is a virus that was proposed to be imported for use in human clinical trials as one of the active ingredients of a vaccine and was assessed according to the requirements for Schedule 1 of the NSNR(O), which applies to “manufacture or import of new microorganisms for introduction anywhere in Canada” (which is the appropriate Schedule for human clinical trials). Living organisms notified under this schedule may be eligible for addition to the Domestic Substances List (DSL).

Regulatory decision

Based on the assessment described below, import of Ad26.Mos1.Env is not considered to be harmful to human health or the environment for the intended use as one of the active ingredients of an investigational vaccine for prevention and treatment of *human*

immunodeficiency virus (HIV-1) infection. As Ad26.Mos1.Env is not entering the environment in a quantity or under conditions that pose a danger to the environment or human health, no further action is recommended as a result of this assessment. After April 17, 2018, the import of Ad26.Mos1.Env could proceed in Canada. This substance is eligible to be added to the DSL.

Background

Ad26.Mos1.Env is genetically modified. The modifications render the micro-organism incapable of replication, and allow it to contain a modified combination of several genes derived from HIV-1 (i.e. synthetic transgenes). Treatment with Ad26.Mos1.Env (as one of the active ingredients of the investigational vaccine) would lead to production in the human body of HIV-1-specific antigens, which are expected to help stimulate an improved immune response against HIV-1 and thereby prevent HIV infection or treat an existing HIV infection.

Hazard considerations

The hazard potential of Ad26.Mos1.Env is considered to be low for the following reasons:

- Deletion of the viral replication gene in Ad26.Mos1.Env impairs replication, thereby diminishing its virulence, as demonstrated in data from pre-clinical studies provided by the notifier. Procedures used to generate Ad26.Mos1.Env prevent the formation of replication-competent adenovirus and testing is done to ensure that replication-competent virus is not present in the final vaccine product.

- The genetic modifications are well-defined and stable. The probability of Ad26.Mos1.Env reverting to the wild type or to a virulent strain in natural environments is low.

- The host range of the wild-type human adenovirus is limited to humans and a few mammalian species (Wold and Horwitz 2007). There is no evidence to suggest that wild-type human adenovirus can infect plants, invertebrates or aquatic vertebrates.

- Wild-type human adenovirus is ubiquitous in the environment and rarely causes disease in humans (Wold and Toth 2013). The wild-type ancestor of Ad26.Mos1.Env has been reported to cause diarrhea and acute meningoencephalitis in immune-

compromised hosts (Hierholzer 1992; Dubberker et al. 2006). Conjunctivitis was reported in immune-competent hosts (Bialasiewicz 2007).

- In the unlikely event that Ad26.Mos1.Env reverts to its original virulence, effective antiviral drug treatments are available.

Exposure considerations

The environmental and human exposure potential from import of Ad26.Mos1.Env for investigational use is considered to be low for the following reasons:

- A small quantity of Ad26.Mos1.Env will be imported into Canada for the purposes of the investigational study for use as one of the active ingredients of a vaccine.

- Procedures are in place to minimize the environmental release of Ad26.Mos1.Env during the clinical trial. Due to the non-replicative nature of Ad26.Mos1.Env shedding is not anticipated and the intra-muscular route of administration further reduces the potential for shedding

- In the event that the vaccine is licensed, the imported quantity is expected to increase. Similar procedures are expected to be in place at locations where it could be administered and exposure to environmental species and humans is not expected to change.

- Ad26.Mos1.Env is not capable of replication and therefore it is unlikely that it can disseminate into the environment.

- There is no evidence indicating that the modified genes in Ad26.Mos1.Env will alter the invasiveness potential of the virus or allow it to disperse or disseminate widely in the environment.

- Ad26.Mos1.Env will only be imported into Canada as part of the final vaccine product and no manufacture is anticipated in Canada. In the event that manufacture commences in Canada, manufacturing procedures and quality control measures will be in place which would effectively limit releases of the notified organism into the environment.

Risk assessment conclusion

Risk is typically described as the probability of an adverse effect occurring based on hazards and a particular scenario of exposure (Environment Canada and Health Canada, 2011). Exposure scenarios can be described based on intended and any potential uses. In the present case, Ad26.Mos1.Env will be imported and used as an investigational vaccine or as an approved and commercialized drug.

With respect to the environment (as an investigational vaccine)

Given the low potential environmental hazard and the low potential environmental exposure, the environmental risk associated with the use of Ad26.Mos1.Env as an investigational vaccine is considered low.

With respect to human health (as an investigational vaccine)

Given the low potential human health hazard and the low potential human exposure, the human health risk associated with the use of Ad26.Mos1.Env as an investigational vaccine is considered low.

With respect to environment and human health (as an approved and commercialized drug)

Should Ad26.Mos1.Env be approved and commercialized for use in Canada for prevention and treatment of HIV-1 infection, the environmental and indirect human exposure is not expected to change significantly, and so would not significantly increase environmental or human health risks.

References

(excluding proprietary information or references provided by the notifier)

Bialasiewicz, A. (2007). Adenoviral keratoconjunctivitis. Sultan Qaboos University Medical Journal, *7*(1), 15-23.

Dubberke, E.R., Tu, B., Rivet, D.J., Storch, G.A., Apisarnthanarak, A., Schmidt, R.E., Weiss, S. and Polish, L.B. (2006). Acute meningoencephalitis caused by adenovirus serotype 26. Journal of neurovirology, *12*(3), 235-240.

Environment Canada and Health Canada (2011). Framework for Science-Based Risk Assessment of Micro-organisms Regulated under the Canadian Environmental Protection Act, 1999. (viewed January 2019).

Hierholzer, J.C. (1992). Adenoviruses in the immunocompromised host. Clinical microbiology reviews, *5*(3), 262-274.

HIV.gov (2019). What Are HIV and AIDS? (viewed January 2019).

Wold, S.M. W. and Toth, K. (2013). Adenovirus vectors for gene therapy, vaccination and cancer gene therapy. Current gene therapy, *13*(6), 421-433.

Wold, W., and Horwitz, M. (2007). Adenoviruses. Fields Virology *2*, 2395-2436.