Risk Assessment Summary

for

NSN 18831: DTX301

(For use as an investigational gene-therapy vector for treatment of ornithine transcarbamylase deficiency in humans)

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)] must be submitted before they are manufactured or imported, and Environment and Climate Change Canada (ECCC) and Health Canada (HC) must assess their potential to harm human health and the environment.

DTX301 is a virus that was proposed to be imported for use in human clinical trials of an investigational gene therapy and was assessed according to the requirements for Schedule 1 of the NSNR(O), which applies to “manufacture or import of new micro-organisms 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 DSL.

Regulatory Decision

Based on the assessment described below, import of DTX301 is not considered to be harmful to human health or the environment for the intended use as an investigational gene-therapy vector for treatment of ornithine transcarbamylase deficiency which is an inherited disorder that causes ammonia to accumulate in the blood (NIH, 2018). As DTX301 is not entering the environment in a quantity or under conditions that pose a danger to the environment or humans, no further action is recommended as a result of this assessment. After December 16, 2016, the import of DTX301 could proceed in Canada. This strain is eligible to be added to the DSL.

Background

DTX301 is a genetically modified virus (human adeno-associated virus “AAV”). The modifications render the micro-organism incapable of replication (making it unable to cause disease), and allow it to transfer a synthetic ornithine transcarbamylase (OTC) gene to human liver cells. Treatment with DTX301 should increase OTC activity, which is deficient in the study subjects. OTC promotes the removal of ammonia from the blood.

Hazard Considerations

With respect to the environment
The environmental hazard potential of DTX301 is considered to be low for the following reasons:

- Wild-type AAV is not prevalent in aquatic plants, invertebrates, vertebrates, or terrestrial plants or invertebrates.

- Despite its wide-spread occurrence in a number of terrestrial vertebrate species (Calcedo and Wilsom, 2013), there is no report of pathogenicity or adverse effects of AAV or any of its derivatives in terrestrial vertebrates in the literature.

With respect to human health
The human hazard potential of DTX301 is considered to be low for the following reasons:

- Despite the wide-spread occurrence of wild-type AAV in humans, and over three decades of history of use of its recombinant derivatives in gene therapy trials, there are no reports of pathogenicity or adverse effects of the wild-type AAV or its derivatives in the literature (Gao et al. 2002; Davidoff et al. 2005, Jiang et al. 2006, Nathwani et al. 2006, Nathwani et al. 2007, Nathwani et al. 2011). The notifier provided surrogate data from clinical trials using another recombinant AAV strain, DTX101. Results of these clinical trials confirmed that recombinant AAV did not have any sustained hepatotoxicity or other adverse effect.

- In case of the AAV transgene vectors, the lack of T-cell activation against the transgene product combined with low levels of pre-existing neutralizing antibodies in human populations minimizes their inhibition after in vivo transduction. In addition, given the reduced level of impurities (i.e. empty capsids) in the DTX301 product, the

possibility of adverse immune reactions, as previously seen in other gene therapy programs, is reduced if not eliminated (Gao et al. 2014).

The following considerations were also taken into account in the assessment of human health and environmental hazard

- Genetic modifications in DTX301 are well-defined and stable. The inserted OTC expression cassette leads to the production of an OTC enzyme in host cells that catalyzes the conversion of ornithine to citrulline in the urea cycle. The OTC enzyme does not have any known pathogenic or toxic properties.

- DTX301 strain is replication-incompetent and does not cause typical wild-type AAV infection. It would require the help of two additional viruses for replication and packaging. Infection of a target cell under natural conditions with three different viruses is extremely unlikely.

Exposure Considerations

With respect to the environment and humans
The environmental and human exposure potential from import of DTX301 for investigational use is considered to be low for the following reasons:

- The proposal for a clinical trial only targets two patients in Canada.

- Procedures are in place to minimize the environmental release of DTX301 during the clinical trial, including intravenous administration at a clinical site under controlled conditions, with treatment of all virus-contact waste by autoclaving, incineration or chemical disinfection.

- The non-replicating nature of DTX301 precludes any viremia in the infected individual and any further dissemination of the virus.

- There is a low potential for shedding of infectious particles. Instructions are provided to patients on how to minimize the dissemination of any shed virus and its exposure to household contact surfaces.

- No potential use has been described for DTX301 other than commercialization as a gene therapy for OTC deficiency. Should it be commercialized as a treatment for OTC deficiency, it is estimated that only 692 patients may potentially benefit from the

treatment and therefore Canadian exposure to DTX301 through household contacts or through other environmental exposures would not significantly change.

- DTX301 is not manufactured in Canada. If it were, exposure of Canadians through environmental exposure would not significantly increase; as the current methods described for the manufacture of DTX301 closely align with containment level 2 (CL2) procedures described in the Canadian Biosafety Standard, which would effectively prevent 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, DTX301 will be imported and used as an investigational gene therapy vector or as an approved and commercialized drug.

With respect to the environment (as an investigational gene therapy)
Given the low potential environmental hazard and the low potential environmental exposure, the environmental risk associated with the use of DTX301 as an investigational gene therapy vector is considered low.

With respect to human health (as an investigational gene therapy)
Given the low potential human health hazard and the low potential human exposure, the human health risk associated with the use of DTX301 as an investigational gene therapy vector is considered low.

With respect to environment and human health (as an approved and commercialized drug)
Should DTX301 be approved and commercialized for use in Canada for treatment of OTC deficiency, 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)

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