Animate virus-like particles (VLPs) and sub-viral particles (SVPs) subject to *New Substances Notification Regulations (Organisms)*

The purpose of this advisory note is to communicate the New Substances program's interpretation of the terms "virus-like particles" (VLPs) and "sub-viral particles"(SVPs) in paragraph (b) of the definition "micro-organism" described in subsection 1(1) of the *New Substances Notification Regulations (Organisms)* [the Regulations]. The Regulations under Part 6 of the *Canadian Environmental Protection Act, 1999* (the Act), which specifically applies to the manufacture and import of new animate products of biotechnology (living organisms).

Background

In the scientific literature, the terms VLP and SVP are applied to a diverse range of substances, including:

- unidentified particles resembling viruses (Dane & Moya, 1965; Molyneux, 1974);
- virus particles packaged with nucleic acids such as small interference RNAs or micro-RNAs (Fang, *et al.*, 2018);
- viruses that contain modified viral genomes (Schlom *et al.*, 1971; Akahata *et al.*, 2010); or
- empty cell membrane envelopes or capsids that resemble the external structure of a virus (Jiang *et al.*, 2016; Hu & Liu, 2017).

Recent scientific definitions have classified VLPs as engineered genome-free ("empty") viral capsids, or viral envelopes that are replication-deficient (Lindsay *et al.*, 2018). Contemporary vaccine platforms use several expression systems, including bacterial, yeast, insect, plant, and mammalian cells to produce genome-free VLPs and SVPs. Recently, engineered VLP platforms have been used to carry SARS-CoV2 antigens to treat or prevent COVID-19.

Because VLPs and SVPs are included in the regulatory definition of a "micro-organism" in subsection 1(1) of the Regulations, it is important to clarify that the Regulations specifically apply to animate products of biotechnology (living organisms), and to provide an interpretation determining when VLPs and SVPs are considered to be animate and therefore subject to the Regulations.

As a result,

1. VLPs and SVPs that do not encapsulate nucleic acids or a viral genome, and are incapable of replication **are not considered to be animate**, and are thus not notifiable under the Regulations.
2. VLPs and SVPs that encapsulate nucleic acids or a viral genome, or are replication competent **are considered to be animate** and therefore notifiable as **micro-organisms** according to paragraph (b) of the definition of a "micro-organism" in subsection 1(1) of the Regulations.

3. VLPs and SVPs described in point 1 above, may be notifiable as biochemical[1] substances under the *New Substances Notification Regulations (Chemicals and Polymers)*. If not listed on the Domestic Substance List (DSL), notification may be required prior to manufacturing or importing the substance in quantities that exceed 100 kg per year.

Contact Information:
If you have any questions on manufacture or import of VLPs or SVPs and whether they are subject to the Regulations, please contact the Substances Management Information Line:

Telephone: 1-800-567-1999 (toll-free in Canada) or 1-819-938-3232 (outside Canada)
Fax: 1-819-938-5212
E-mail:eccc.substances.eccc@canada.ca

You may also visit the New Substances Website.

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Signed on October 5, 2020

References:

Akahata, W., Yang, Z., Andersen, H., Sun, S., Holdaway, H., Kong, W., . . . Nabel, G. (2010). A virus-like particle vaccine for epidemic Chikungunya virus protects nonhuman primates against infection. *Nature Medicine, 16*(3), 334-338.

Dane, C., & Moya, B. (1965). *Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. The lancet, 295*(7649), 695-698.

[1]As per subsection 1(1) of *New Substances Notification Regulations (Chemicals and Polymers)*, a ***biochemical*** means a substance, other than a polymer, that **(a)** is produced by a micro-organism; or **(b)** is a protein or nucleic acid that is derived from a plant or an animal. (*substance biochimique*).

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Lindsay, B., Bonar, M., Costas-Cancelas, I., Hunt, K., Makarkov, A., Chierzi, S., . . . Rouiller, I. (2018). Morphological characterization of a plant-made virus-like particle vaccine bearing influenza virus hemagglutinins by electron microscopy. *Vaccine, 36*(16), 2147-2154.

Molyneux, D. (1974). Virus-like particles in Leishmania parasites. *Nature, 249*(5457), 588-589.

Schlom, J., Spiegelman, S., & Moore, D. (1971). RNA-dependent DNA polymerase activity in virus-like particles isolated from human milk. *Nature, 231*(5298), 97-100.