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Research review paper

Bringing plant-based veterinary vaccines to market: Managing regulatory and commercial hurdles☆

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ABSTRACT

The production of recombinant vaccines in plants may help to reduce the burden of veterinary diseases, which cause major economic losses and in some cases can affect human health. While there is abundant research in this area, a knowledge gap exists between the ability to create and evaluate plant-based products in the laboratory, and the ability to take these products on a path to commercialization. The current report, arising from a workshop sponsored by an Organisation for Economic Co-operation and Development (OECD) Co-operative Research Programme, addresses this gap by providing guidance in planning for the commercialization of plant-made vaccines for animal use. It includes relevant information on developing business plans, assessing market opportunities, manufacturing scale-up, financing, protecting and using intellectual property, and regulatory approval with a focus on Canadian regulations.

Abbreviations: AFD, Animal Feed Division; ANVISA, National Health Surveillance Agency; APHIS, Animal and Plant Health Inspection Service; APVMA, Australian Pesticide and Veterinary Medicine Authority; BIS, Bureau of Indian Standards; CCVB, Canadian Centre for Veterinary Biologics; CEO, chief executive officer; CFIA, Canadian Food Inspection Agency; CFO, chief financial officer; CONABIA, National Agricultural Biotechnology Advisory Committee; COO, chief operating officer; CSO, chief scientific officer; CTNBio, National Technical Commission on Biosafety; DAFF, Department of Agriculture, Forestry and Fisheries; DBT, Department of Biotechnology; EC, European Commission; EFSA, European Food Safety Authority; EMA, European Medicines Agency; FDA, Food and Drug Administration; FSSAI, Food Safety and Standards Authority of India; FTO, freedom to operate; GAQSIQ, General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China; IP, intellectual property; MAPA, Ministry of Agriculture, Livestock, and Food Supply; MOA, Ministry of Agriculture; MOAC, Ministry of Agriculture and Cooperation; MOEF, Ministry of Environment and Forests; MOHFW, Ministry of Health and Family Welfare; MOST, Ministry of Science and Technology; NSS, National Surveillance System; OAGEBA, Office of Agricultural Genetic Engineering Biosafety Administration; OECD, Organisation for Economic Co-operation and Development; OGTR, Office of the Gene Technology Regulator; PCT, Patent Cooperation Treaty; PBO, Plant Biosafety Office; SAGPyA, Secretariat of Agriculture, Livestock, Fishery, and Food; SENASA, National Service of Health and Agrifood Quality; USDA, United States Department of Agriculture.

☆ The opinions expressed and arguments employed in this publication are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its Member countries.

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Contents

1. Introduction

The animal health field provides a unique opportunity for the application of plant-derived immunotherapeutics and vaccines. Infectious diseases have historically been a major cause of economic loss to the livestock industry worldwide, both directly as well as through disruptions in international trade. For example, bovine spongiform encephalopathy (mad cow disease) cost the Canadian beef and dairy industries over $5.3 billion in the two years following the identification of the first infected animal (Statistics Canada, 2006). Likewise, there are numerous other zoonotic pathogens, such as *Escherichia coli* O157, which do not affect the health of animals yet result in economic losses due to outbreaks of disease in human populations. A growing desire to control such pathogens is evident in public health initiatives such as One Health <www.onehealthinitiative.com/>, an international effort to expand collaboration across healthcare for humans, animals, and the environment. Of course, a multitude of economically important veterinary diseases exist that are not of significant risk to humans: notably foot-and-mouth disease, Newcastle disease, classical swine fever, porcine reproductive and respiratory syndrome, and porcine epidemic diarrhea.

Vaccines have the potential to reduce the burden of animal infections, but in many cases vaccines have not been produced that are both effective and cost-saving for the livestock industry. For example, a vaccine against *E. coli* O157 (Canadian license issued in 2008, now inactive) for use in cattle has a projected capacity to reduce human cases by nearly 85%, yet adoption of this vaccine by farmers was low (Matthews et al., 2013). Low adoption rates were due both to the cost of the vaccine and the need to handle animals three times for vaccine administration. Production of lower-cost vaccines in plants combined with oral administration by incorporating the product into livestock feed may be an avenue to increased adoption.

Although the concept of plant-derived veterinary vaccines dates back to 1993 (Usha et al., 1993), such vaccines are yet to be available on the market. Interest in the use of transgenic plants for pharmaceutical production has been growing over the past five years (Fig. 1); and interest in veterinary vaccines, in particular, has been increasing because regulatory approval can be significantly less onerous than that for human pharmaceuticals (Phan et al., 2013). The motivation for production of vaccines and other biologics from plants arises from an array of potential advantages over other production systems (Kolotilin et al., 2014). Depending on the plant system used, these advantages can include relatively high expression levels; effective post-translational modifications including proper folding and glycosylation; lower risk of contamination with animal pathogens or bacterial toxins; cost-of-production efficiencies; speed of development in the case of transient expression; stable, room temperature storage within seeds and oral administration of the product (Everett et al., 2012; Kolotilin et al., 2012; Tremblay et al., 2010).

Plant production platforms are diverse, and may involve the use of whole plants in a greenhouse or field, or plant cell culture; stable or transient expression; targeted or constitutive expression; expression from nuclear or organelle genomes; and expression of protein monomers, multimers, or virus-like particles. In addition, the unmodified version of the engineered plant may be a food or feed crop, or neither. The product may be intended for purification, or administration as a crude extract or whole plant tissue, and the planned route of administration may be oral, nasal, topical, or through injection. These factors all influence the advantages of the plant-based system, and can affect the steps in the commercialization process of a potential plant-made product. For example, while oral immunization is likely to be more convenient for the end-user, it often necessitates a very large dose to elicit the desired response, requiring milligram or gram quantities as opposed to the micrograms needed for injectable delivery (Rybicki, 2010).

Several excellent references for varied topics of interest for the commercialization of plant-made pharmaceuticals have recently been published. For products and platforms, a large array of plant species and

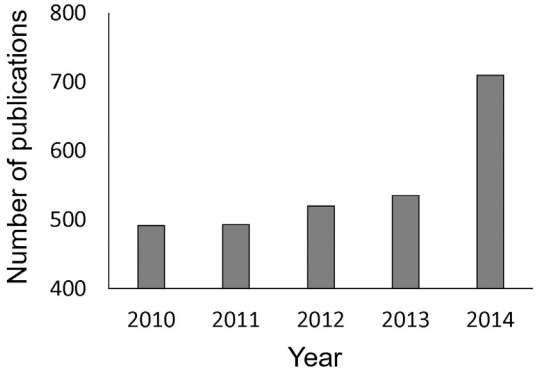

Fig. 1. Number of published articles on plant-made vaccines over the last five years (2010–2014). Articles were retrieved for each year using the search term "transgenic AND plant AND vaccine" in SpringerLink, ScienceDirect, Wiley, and Web of Science, and combined from all sources.

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