Key regulatory considerations for veterinary vaccine development in the EU and the US

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Keywords/Abbreviations

Veterinary Vaccine; Veterinary Immunological; Veterinary Biological; Regulatory; EU; US; Legislation; Marketing Authorisation (MA); US Veterinary Biological Product License; Scientific Advice (SA); Committee for Medicinal Products for Veterinary Use (CVMP); Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv); Member State (MS); National Competent Authority (NCA); Summary of Product Characteristics (SPC); Innovation Task Force (ITF); Ad hoc Group on Veterinary Novel Therapies (ADVENT); Proof of Concept (POC); Research & Development (R&D); Good Manufacturing Practice (GMP); Good Laboratory Practice (GLP); International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal products (VICH); European Pharmacopoeia (Ph. Eur.); United States Pharmacopoeial Convention (USP); Veterinary Services Memorandum (VSM); Formulation; Safety; Efficacy; Small and Medium Sized Enterprises (SMEs) and Limited Markets.

Abstract

Developing and registering a veterinary vaccine for the global market can be challenging. A product registration in the European Union (EU) and/or the United States of America (US) is considered by many in the animal health industry as the key to unlocking other global markets. There are some important differences in the regulatory requirements for licensing veterinary vaccines in the EU and US, and this will be the focus of this article. However, with extensive up-front planning, it is possible to minimise the additional cost and time required to satisfy the requirements for both of these major markets. The key regulatory issues that should be considered when planning a development plan for the EU and US are discussed.

Introduction

According to the Health for Animals 2014 report[1], biological veterinary medicinal products represent about 26% of the global market for veterinary medicines. Currently, the European and US markets collectively account for more than 70% of the global veterinary vaccine market revenue (Future Market Insights, 2016[2]). Although considerable investment in the vaccine sector in South America and Asia is likely to result in growth in these markets, for the foreseeable future, gaining regulatory approval in the EU and/or US is likely to remain a significant achievement in terms of global sales for a veterinary vaccine.

Definitions and Legal Framework

Vaccines are regulated as 'veterinary biologics' in the US, along with a wide range of prophylactic, therapeutic and diagnostic products. This includes bacterins and bacterial extracts, toxoids, antibody products, immunomodulators, serum and plasma products, antitoxins, allergens and diagnostic kits (9 CFR, Part 101.2[3]). In the EU, the equivalent key legislation for immunological veterinary medicinal products (IVMPs) is technically restricted to vaccines and serum (Directive 2001/82/EC[4]; Title I, Article. 1.7) but the principles may also be applied to other biologically derived products where scientifically justified.

Veterinary vaccines fall under the jurisdiction of the United States Department of Agriculture (USDA) where they are regulated by the Animal and Plant Health Inspection Service - Center for Veterinary Biologics (APHIS-CVB). The CVB is responsible for the scientific evaluation in accordance with the Virus-Serum-Toxin Act of 1913[5]; specific requirements are outlined in Title 9 of the Code of Federal Regulations (9 CFR) and guidance documents including Veterinary Services Memoranda[6] (VSM).

The principal legislative framework that applies to all IVMPs in the EU is laid down in the European Community Code (Directive 2001/82/EC[4], as amended by 2004/28/EC[7] and 2009/9/EC[8]). It should be noted that this legislation is currently under review and should be repealed by a new EU Regulation[9] within the next few years. Product specific requirements are further defined by supplementary legislation and by the European Pharmacopoeia (Ph.Eur.). In addition, Guidelines, Recommendations and Opinions aim to inform applicants and National competent authorities (NCAs) on the most appropriate way to fulfil obligations in the legislation; however these are not legally binding and this in part contributes to a complex regulatory picture in the EU.

The options available with regards to 'route to market' in the EU are more extensive than in the US and are outlined in **Table 1**. A 'Marketing Authorisation' (MA) at the European or National Member State (MS) level is granted when a positive benefit:risk balance has been demonstrated for the product.

Pharmaceutical VMPs are typically considered to be 'globally portable' in regulatory terms as there is greater harmonisation in the regulatory requirements between the EU and US and in general there are fewer geographical and epidemiological constraints. As a result it is possible to seek joint scientific advice and largely align the development plan within these key markets. In contrast, for vaccines, only the general principles (demonstration of efficacy, safety, purity, potency and consistent manufacturing) are common to vaccine product developments. A product license is granted after demonstration that the product can be manufactured and tested to a consistent quality standard, and that the benefits of the product in terms of the efficacy outweigh any associated safety risks. However, the way in which this is demonstrated is not aligned in the EU and US. The need to accommodate a number of important differences in a single development plan (in order to satisfy alternative requirements) can quickly become difficult to manage. No matter how minor the individual differences appear, together they can lead to significant cost and logistical implications, often meaning that two almost entirely separate developments may need to be undertaken.

Table 1: Regulatory Strategy / Routes to Market in the EU

EU Regulatory Procedure	Associated Time & Costs	Marketing Authorisation (MA) Outcome and Dossier / Product Information Harmonisation
Centralised (CP) Evaluated by the CVMP	18 months 1 fee	1 MA across the EU Dossier & SPC fully harmonised
Decentralised (DCP) Co-ordinated by CMDv	18 months A fee for each MS	1 MA in each MS Dossier fully harmonised, SPC largely harmonised
National	15 - 36 months varies 1 fee	1 MA
Mutual Recognition (MRP) Co-ordinated by CMDv	National timeline + 9 months A fee for each MS	1 MA in each MS Dossier and SPC largely harmonised

As consultants for biological products in the EU, US and Canada, we often get asked 'is it possible to develop a particular veterinary biological for the global market'?

The short answer is that it depends on the vaccine. Epidemiological constraints (strain relevance) mean that it may not be possible for some products. Companion animal vaccines tend to be more globally adaptable than vaccines for food producing species, where different animal husbandry practices also need to be taken into account. Some key considerations when developing a veterinary vaccine for the EU and US markets are outlined below.

The Development Plan

A detailed and structured plan from the outset is essential for ensuring a successful vaccine development.

The availability of defined guidelines and monographs facilitate the process for more conventional products. However where legislation is not aligned, is absent, or where a product does not easily fit within the existing framework, the regulatory pathway can be uncertain and costly, in terms of both time and budget. Over recent years the regulatory agencies have acknowledged this challenge and have worked towards reducing this uncertainty by establishing a variety of advisory groups that provide an opportunity to discuss the best approach (in principle) for a product's development (see **Table 2** for further details).

In the US, licensing of veterinary vaccines by the USDA APHIS is accomplished by 'phased submission', which has the benefit of consultation and agreement at each phase (and there are no associated costs). An assigned CVB reviewer will provide comments on the applicant's licensing plan and pivotal study protocols (for efficacy, safety and stability), and proposals to generate key supporting data (such as inactivation kinetics, maternal antibody interference, potency test and reference validation etc.) before the work starts.

There are a number of areas where the requirements of USDA are not aligned with the EU requirements. Therefore seeking the advice of all interested parties at the start of the process will be beneficial for the success of the development project. *However, it's not only a case of knowing who to ask, but also how to ask the right questions in order to get the required answers.*

Key Issues to Address Early in the Development of a Veterinary Vaccine

- **Antigen / Active Ingredient Selection**

For conventional vaccines, antigen selection is the single most important factor that determines whether a product can be developed for the global market or not. The strain/serotype must be relevant for each geographical region in which the product will be marketed and it is the responsibility of the applicant to justify why it should be considered relevant.

Early research and development (R&D) studies that demonstrate efficacy against circulating strains relevant to each of the markets should be considered. If several challenge models need to be established for several circulating strains or serotypes due to strain divergence this may be prohibitive for a global plan.

- **Starting Materials**

In the EU, Ph.Eur. grade materials must be used where available; whereas in the US, United States Pharmacopoeial Convention (USP) grade materials are not always required for vaccines. This difference in the standard and cost of goods may in part contribute to a decision to establish separate manufacturing sites when producing products for these two markets.

- **Seed Materials**

Antigen production should be based on a seed lot system which has been validated in the pivotal studies. However, during the early proof of concept (POC) development phase, it is not necessary to have an established seed lot system in place, as long as a well characterised research seed is used. As soon as POC has been demonstrated, investment can be made to establish and test a seed lot.

Given that the regulatory requirements and quality standards for the establishment and testing of seed lots vary considerably between the EU and US, it may be more cost effective to establish a separate working seed lot (based on the same master seed lot) in each territory. For example a working seed lot should be established and tested to GMP in the EU, but not in the US. A GMP master seed lot may also be required in the EU if the product is particularly high-tech.

Table 2: Summary of Options for Seeking Regulatory Guidance in the EU

Scientific Advice (SA)[10]	The Scientific Advice Working Party (SAWPv) based at the EMA provides formal advice to companies seeking clarification on the suitability of their intended tests and studies. There is a fee which is reduced considerably for micro, small and medium-sized enterprises (SMEs) and for companies developing products for Minor Use Minor Species (MUMS) / Limited Markets (LM). Whilst the advice provided isn't legally binding, the applicant has the reassurance that they are working towards a scientifically justifiable approach. It is possible to request discussion between the USDA and EMA, although a formal procedure is not currently in place.
Innovation Task Force (ITF)[11]	The ITF is available for companies of any size wishing to obtain informal guidance early in the product development process. The ITF provides support on regulatory, technical and scientific issues arising from the development of innovative medicines. The meetings are free of charge.
Ad Hoc Group on Veterinary Novel Therapies (ADVENT)[12]	This (newest) initiative was established at the EMA in 2014. The remit of this group's work is to provide general guidance (not product specific) on novel therapies in the form of 'Questions and Answers' on topics of most interest to industry.

- **Product Formulation**

Consideration should be given to the final product formulation early in the development process and how representative this will be for the product to be licensed. Early POC studies are typically conducted using small-scale research batches to establish the formulation. From this point on, R&D batches should closely resemble the anticipated final formulation in order to avoid the need to repeat key studies, and it is recommended that the final formulation is decided prior to starting any pivotal studies.

Due to the phased submission process in the US, there are additional requirements for formulation of vaccine for use in pivotal studies. For example, vaccine serials must be prepared using a Master/Working seed lot and the outline of production that has already been approved by the CVB.

In both territories, the pros and cons of introducing a novel adjuvant should be given serious consideration, particularly if the vaccine is intended for a food producing species. If a new adjuvant is used, a significant amount of additional safety data may be required to support licensing, even if establishment of a Maximum Residue Limit (MRL) is not required. A decision should therefore be taken early on, as to whether the benefit of the novel adjuvant outweighs the cost implications for its inclusion.

- **Quality Control Analytical Methods**

Ideally, a draft specification should be established early in the development process in order to ensure that it is possible to demonstrate that early R&D batches, pivotal study batches and consistency batches are essentially equivalent. A comprehensive range of characterisation tests should be included (but not necessarily limited to) the tests specified in the legislation. Establish the necessary analytical methods (including potency) with, at a minimum, a basic validation in place as soon as possible. It's much easier to do more tests initially in order to fully characterise the product and remove redundant tests later.

- **Manufacturing Sites and Quality Standards**

The manufacturing site(s) should be selected with care. If a single site is intended to be used for manufacture of the US and EU products, the manufacturing facilities for the antigen and finished product must be inspected and approved by both relevant authorities. To satisfy the EU requirements, the site should hold a manufacturing license and have been inspected for GMP by a relevant EU competent authority. For the US, USDA domestic manufacturing sites must hold a US Veterinary Biologics Establishment License, and both foreign and domestic manufacturing sites are subject to annual inspection by the Inspection and Compliance division of CVB.

Facilities that manufacture biological products in the US are required to pass an inspection in accordance with 9 CFR; whereas pharmaceutical manufacturers are inspected in accordance with the more stringent 21 CFR Part 211 Current Good Manufacturing Practice (cGMP)[13] which is more in line with EU GMP requirements[14]. However US 'cGMP' certification cannot be used as a substitute for an EU 'GMP' as a mutual recognition agreement of GMP inspections does not exist between the EU and the US.

- **Safety and Efficacy Studies**

At first glance, the requirements for the demonstration of safety and efficacy seem to be quite similar, but a more detailed review shows this is not really the case. In the EU, laboratory safety studies for single dose, repeated dose (and overdose for live vaccines) are required and these should be conducted according to Good Laboratory Practice (GLP). Whilst VICH GL44[15] (Target Animal Safety of Veterinary Vaccines) applies in both the EU and US, it is appended to VSM 800.207[16] in the US, and this guidance describes a different interpretation of how requirements are met compared to that described in the EU Ph.Eur. monographs. For example, the quality standard required is not specifically defined in the VSM, and single and repeat dose safety is deemed by APHIS-CVB to be adequately demonstrated in the field safety study. Reversion to virulence studies for live vaccines also differ in their requirements between these territories; as do the EU monograph requirements and 9 CFR relating to the conduct of challenge studies. In general, the number of animals required in the US is higher and specified routes of administration and pass/fail criteria may also be quite different.

Regarding field studies, the EU guidance requires a minimum of two geographically distinct regions (located in the EU) for conduct of field studies; a combined safety and efficacy study is also acceptable. In contrast, the USDA requires a minimum of three geographically distinct field study sites for the demonstration of safety, one of which may be in a VICH country outside the US. Another major difference is that a field efficacy study is normally required for the EU whereas it is seldom required for the US (note product-specific requirements may be imposed). Therefore the development budget must include provision for conduct of multiple field studies in order to register in both territories.

Small and Medium Sized Enterprises (SMEs) and Limited Markets

SMEs can be just as successful as the multi-nationals in the development of veterinary vaccines for major markets provided appropriate care is taken with regards to strategy and project planning. In the EU, SMEs are encouraged to develop VMPs through the provision of additional administrative and procedural assistance, including fee reductions, exemptions or deferrals for certain administrative services (such as 90% fee reduction for scientific advice and free product literature translation at the end of the procedure). There are no fees for regulatory submissions or scientific advice for licensing of veterinary vaccines and other biologics by the USDA.

It is particularly important for SMEs to decide which territory (EU or US) will take the lead in such a development. This is especially important when there is a need to generate revenue as soon as possible in order to fund the completion of additional studies to support future geographic expansion.

In terms of developing products for Limited Markets, the EMA's policy regarding Minor Use Minor Species (MUMS; EMA/308411/2014 adopted[17]) is aimed at stimulating development of new VMPs for minor species and for rare diseases in major species which may not be otherwise developed. The CVMP's guideline on 'Data Requirements for Immunological Veterinary Medicinal Products intended for Minor Use or Minor Species/Limited Markets' (EMA/CVMP/IWP/123243/2006-Rev.2[18]) provides a list of all the reduced data requirements from Annex I of Directive 2001/82/EC as amended by Directive 2009/9/EC[8], which may be acceptable for products successfully registered for MUMS (although acceptability is determined on a case by case basis). There are also considerable financial incentives for developing MUMS VMPs indicated for food producing species where no alternative product is authorised. However it should be noted that "MUMS" categorisation is not recognised at the USDA.

The US has a mechanism for meeting limited markets (including emergency conditions, local situations, or other special circumstances) through the issuing of a Conditional License (under 9 CFR 102.6[19]). Data requirements are reduced in that a "reasonable expectation of efficacy" is acceptable, and full validation of the potency test may be "pending" at the time the license is issued. However, should subsequent studies demonstrate efficacy failure, the conditional licence would not be renewed and there are no reductions in the requirements for safety or purity data. It is important to note that a conditional license is not applicable to imported products; domestic manufacturing arrangements are a pre-requisite for this license.

Similarly, many of the EU Member States have their own provision for registering vaccines in exceptional circumstances and for limited markets, where reduced data requirements are applied. However, as these requirements are established at a National level by each NCA, this subject is too complex to be explored within the limited scope of this article.

Maintain a Dynamic Development Plan and Never Stop Reviewing Progress

Good planning up front is only one part of a successful development for key global markets. It's crucial to maintain a dynamic development plan and to continuously monitor progress. Vaccine development projects typically span a number of years during which time changes in the legislation and guidance may arise, so it's important to track and update the original plan as the project progresses. Engagement of the entire development team is also key to ensure a common understanding of the issues and the end goal so that correct decisions are made as and when issues inevitably arise.

Conclusion

The basic principles of demonstration of purity, safety, efficacy, and potency of vaccines are common to many markets around the world. However, there is sufficient divergence in the acceptable approaches for meeting these criteria in the various countries to make global vaccine development a significant challenge. However, with careful planning and consideration of the regulatory requirements it is possible to reduce repetition, cut costs and streamline the development to achieve the ultimate goal of obtaining licenses in multiple major markets.

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