

Veterinary vaccine registration: Global regulatory standards, harmonization, and approval challenges

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Abstract

The global demand for veterinary vaccines is growing due to the rising incidence of transboundary animal diseases and the increasing recognition of animal health as a cornerstone of public and environmental well-being. Central to this effort is a robust and well-defined vaccine registration process, which ensures that products entering the market meet established standards of safety, quality, and efficacy. Despite progress, the veterinary regulatory landscape remains fragmented, with varying protocols, timelines, and expectations across countries and regions. This review critically examines global regulatory frameworks and key data requirements involved in veterinary vaccine development and approval, including the roles of key bodies such as the World Organisation for Animal Health (WOAH), the European Medicines Agency (EMA), and the USDA. Critical regulatory elements such as preclinical studies, efficacy trials, safety assessments, and manufacturing controls are discussed. The review further explores efforts toward harmonization through initiatives like VICH and One Health, emphasizing the importance of international collaboration and innovation. By synthesizing current knowledge and regulatory practices, it aims to inform policymakers, researchers, industry stakeholders, and regulatory bodies, fostering efforts toward harmonized, science-based, and adaptive regulatory frameworks. Future directions recommend investing in digital regulatory tools, developing emergency approval frameworks, and strengthening veterinary-specific infrastructure to ensure prompt access to safe and effective vaccines globally. The review underscores the urgent need for adaptive, science-based regulatory systems that can support rapid vaccine deployment in the face of emerging animal health threats.

Keywords: animal health, global regulatory standards, regulatory challenges, vaccine approval processes, veterinary vaccine regulation

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Introduction

Importance of veterinary vaccines in public health, food security, and zoonosis prevention: Veterinary vaccines constitute a cornerstone in the protection and promotion of animal health and welfare, with far-reaching implications for public health, global food security, and the mitigation of zoonotic disease transmission (Saleem *et al.*, 2023). Infectious diseases in animals can cause significant economic losses in agriculture and compromise food supply chains, while many of these pathogens have the potential to spill over into human populations (Espinosa *et al.*, 2020). The effective control and prevention of infectious diseases in livestock and companion animals through vaccination programs not only enhance animal welfare and agricultural productivity but also serve as critical interventions to safeguard human populations from zoonoses, thereby underscoring the interconnectedness of human, animal, and environmental health under the One Health paradigm (Horefti, 2023).

The role of vaccine registration in ensuring safety, efficacy, and quality: The successful deployment of veterinary vaccines hinges on a comprehensive and stringent regulatory framework that governs vaccine registration. Vaccine registration serves as the primary mechanism to assure that immunological products entering the market are safe for animals, efficacious against target pathogens, and manufactured according to high-quality standards (Suryawanshi *et al.*, 2024). Regulatory oversight in veterinary vaccine development and commercialization involves the comprehensive evaluation of preclinical and clinical data, manufacturing consistency, and post-marketing surveillance. These measures are essential to minimize adverse events, ensure sustained vaccine efficacy, and maintain the confidence of all stakeholders, including farmers, veterinarians, policymakers, and the general public (Heldens *et al.*, 2008). Given the diversity of target species, vaccine formulations, and disease contexts, regulatory frameworks must be flexible (adaptive), robust, transparent, and science-driven to effectively safeguard both animal and public health.

Need for regulatory oversight specific to veterinary vaccine development and commercialization: Veterinary vaccines face unique regulatory challenges distinct from those of human vaccines due to the broad diversity of target species, each exhibiting different physiological and immunological characteristics. Additionally, varying epidemiological factors, husbandry practices, and ethical concerns related to animal experimentation require regulatory approaches specifically tailored to veterinary medicine (Adams *et al.*, 2009). Consequently, veterinary regulatory systems must strike a balance between rigorous safety and efficacy evaluations and the practical need for timely vaccine availability, particularly during outbreaks of emerging or transboundary diseases such as African swine fever virus (ASFV), which threaten animal health and international trade (Knight-Jones *et al.*, 2014). This underscores the necessity for adaptable yet

comprehensive regulatory frameworks that facilitate efficient development, approval, and deployment of veterinary vaccines without compromising quality standards.

Scope, significance, and objective: This review critically examines the global landscape of veterinary vaccine registration, with particular attention to regulatory frameworks, species-specific requirements, and regional variations. It highlights the importance of effective regulatory oversight in managing emerging diseases such as ASFV and explores key challenges faced during vaccine development and approval. The paper also aims to provide practical insights for policymakers, researchers, industry stakeholders, and regulatory authorities. The ultimate goal is to support the advancement of harmonized, evidence-based regulatory approaches that ensure timely access to safe and effective veterinary vaccines worldwide, thereby contributing to improved animal health and public safety.

Overview of Veterinary Vaccine Development and Registration

Veterinary vaccine development pipeline: The development of veterinary vaccines is a complex, iterative and multi-stage process designed to ensure the safety, efficacy, and quality of immunological products before they are made widely available (Fig. 1).

The process begins with the identification and selection of potential antigens based on their immunogenic properties and relevance to the target pathogen. In parallel, suitable adjuvants are chosen to enhance the immune response. Adjuvants that enhance the immune response are often incorporated alongside antigens to improve vaccine potency and durability (Olawade *et al.*, 2024; Venkateswaran *et al.*, 2024). These components are then formulated into prototype vaccine candidates. The formulation process involves optimization of the vaccine composition for stability, delivery, and efficacy in the target species (Jain *et al.*, 2015).

Following formulation, vaccine candidates undergo rigorous preclinical evaluation, typically involving in vitro assays and studies in laboratory animal models (in vivo evaluations) to assess preliminary safety, protective efficacy and immunogenicity (Woodland, 2011). Unlike human vaccines, veterinary vaccines often undergo early testing directly in the target animal species, as surrogate models may not accurately replicate protective responses. Successful candidates advance to controlled field trials conducted in the target animal populations, which provide critical data on vaccine efficacy under real-world conditions, dosing regimens, and safety profiles (Francis, 2020). A critical guiding element in this pipeline is the development of a Target Product Profile (TPP), which outlines key attributes such as dosage, delivery method, duration of immunity, safety benchmarks, and intended market, serving as a strategic reference throughout the development lifecycle (Lee and Burke, 2010).

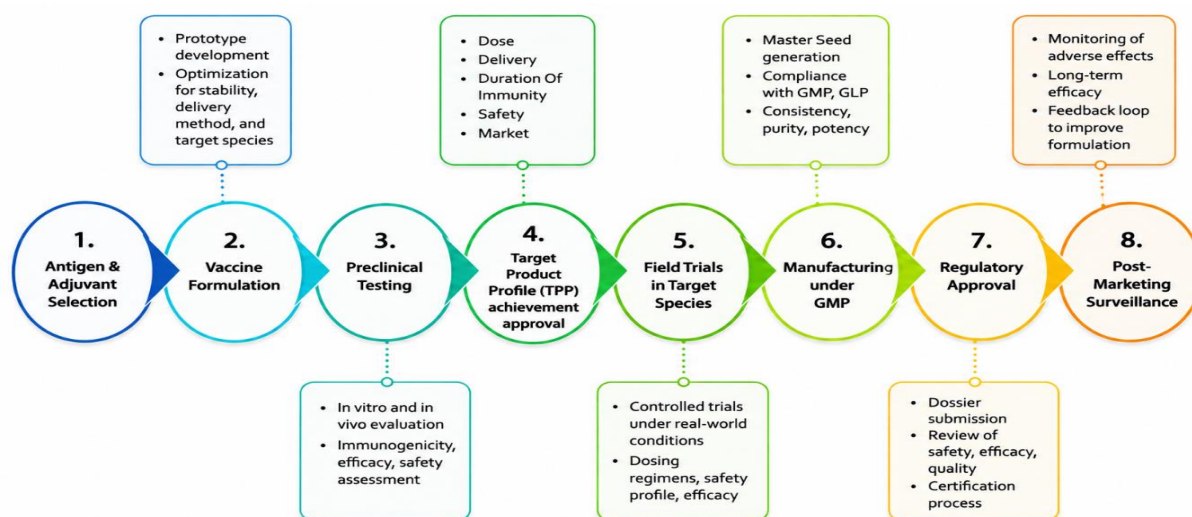


Figure 1 Veterinary vaccine development pipeline.

Upon demonstrating satisfactory results and identifying promising formulations, vaccines enter the manufacturing phase, where processes must comply with stringent quality control and Good Manufacturing Practice (GMP) standards to ensure consistency, purity, and potency across production batches. The GMP guide is structured into three parts: the first outlines the principles for manufacturing medicinal products, the second details the fundamental requirements for active substances used as starting materials, and the third provides guidance on the documentation necessary for regulatory certification. Globally, most countries adopt GMP regulations derived from either the WHO guidelines or the EU guide (Covarrubias *et al.*, 2022). During early-

phase development, this includes the generation of a GMP-compliant Master Seed and the execution of comprehensive safety and efficacy studies under Good Laboratory Practice (GLP). Specific considerations such as potential for reversion to virulence, shedding and spread, and reproductive safety are also assessed, especially for live vaccines. Notably, the veterinary vaccine development process does not follow the phased clinical trial model (Phase I-III) typically observed in human vaccine development (Francis, 2020). Various vaccination strategies can be employed during emergency animal disease outbreaks, and these have been systematically categorized and summarized in Table 1 (Williams, 2007).

Table 1 Vaccination strategies.

Strategy Type	Strategy name	Purpose	Area of application
Purpose-Based	Suppressive Vaccination (Vaccination to kill)	Reduce viral shedding in infected or at-risk animals	Infected zones or areas with immediate exposure risk
	Preventive Vaccination (vaccination to live)	buys time when resources are limited Protect high-risk animals before exposure Depends on vaccine quality and risk level	Clean areas near infected zones In rare or valuable species
Spatial-Based	Barrier (Firebreak, buffer zone)	Form a vaccinated boundary to slow spread Shape influenced by terrain or farm layout	Outside infected zones, guided by geography or animal population
	Ring Vaccination	Encircle infected area with vaccinated animals Common in highly contagious outbreaks Radius depends on disease and resources	Around infected zones; can include premises inside and outside the infected zone(s)
	Targeted Vaccination	Protect high-value or high-risk operations Aims to prevent amplification and protect rare genetic stock	Large farms, feedlots, or conservation zones near outbreaks
	Area/Blanket Vaccination (mass vaccination)	Mass vaccination of all susceptible animals in a defined area. All can mean anything from 70% to 100% depending on the categories that must not or do not need to be vaccinated. Used for large-scale outbreak management	When other measures fail or long-term control is needed

Finally, post-marketing surveillance monitors vaccine performance in the field after regulatory approval, enabling the detection of any adverse events, evaluation of long-term efficacy, and contributing to continuous improvement and public trust (Nwokike, 2023).

This pipeline is iterative and adaptive, with data from each stage guiding subsequent steps to optimize vaccine design and delivery. Integrating strong scientific evidence throughout the development cycle is crucial for meeting regulatory standards and ensuring successful veterinary vaccine approval and deployment. However, several bottlenecks remain, including regulatory complexity, limited GMP manufacturing capacity, and challenges related to intellectual property and funding. Addressing these obstacles early in the development timeline is key to ensuring effective vaccine rollout. The veterinary vaccine development process reflects a holistic, evidence-driven framework that fosters innovation while upholding high standards of safety and efficacy (Kumraj et al., 2022).

Species-specific concerns: Physiological differences, ethical constraints in food and companion animals: Vaccination has been instrumental in effectively controlling species-specific diseases that can devastate local cat and dog populations, such as feline panleukopenia, canine distemper, and parvovirus. Strain-specific vaccines also play a critical role in preventing diseases in livestock and companion animals, with examples including the feline leukaemia virus vaccine for cats and the equine influenza virus vaccine for horses. Additionally, vaccines like the rabies vaccine serve a dual purpose by preventing zoonotic diseases, thereby safeguarding not only domestic animals but also wildlife, livestock, and public health (Badshah et al., 2024).

Given this broad impact, it is important to recognize that veterinary vaccines must account for the unique physiological and immunological characteristics inherent to different animal species. These factors significantly influence vaccine safety, immunogenicity, and overall efficacy (Table 2).

Table 2 Species-specific vaccine challenges.

	Ruminants	Monogastric Avian Species	Companion Animals	Aquaculture Species
Physiological Features	Complex digestive system with rumen; polygastric	Simple digestive system	Typical mammalian physiology	Aquatic physiology
Immune System Dynamics	Unique GALT structure	Different GALT and immune responses	Similar to humans, but species-specific variations	Adapted mucosal immunity for aquatic environment
Vaccine Delivery Challenges	Oral vaccines risk degradation before absorption	Sensitive to adjuvants and antigen doses	Booster schedules need careful consideration	Immersion and oral vaccines preferred
Ethical and Regulatory Issues	Withdrawal periods for meat/milk; safety evaluation for food	Sensitivity to antigen doses; ethical use of cytokine adjuvants; withdrawal periods for meat and eggs	Booster frequency and adverse reaction concerns	Regulatory approval adapted to aquatic environment
Vaccine Safety and Efficacy	Adjuvants may cause adverse reactions if not species-tailored	Potential adverse reactions	Lifelong immunization considerations	Environmental and regulatory challenges

*GALT, gut-associated lymphoid tissue.

Ruminants such as cattle and monogastric avian species like poultry exhibit distinct immune system dynamics and metabolic processes, necessitating tailored vaccine formulations. In ruminants, the complexity of the digestive system, particularly the presence of symbiotic rumen microorganisms and a polygastric structure, poses unique challenges for oral vaccine delivery, as vaccine components may be degraded before reaching effective absorption sites. Furthermore, structural variations in gut-associated lymphoid tissue (GALT) across species influence mucosal immune responses, underscoring the need for species-specific vaccine strategies (Hoelzer et al., 2018). Overcoming these physiological barriers is essential for achieving effective immunization and disease prevention in ruminant species (Herdiana, 2025).

Moreover, an adjuvant or antigen dose deemed safe and effective in cattle may elicit adverse reactions in poultry due to these physiological disparities. Cytokines, a promising class of adjuvant targets known for their potent immunomodulatory

properties, have shown variable effects across species, limiting their widespread commercialization. Their species specificity presents a significant challenge; for instance, IL-10 induces both Th1 and Th2 responses in mice but fails to elicit similar responses in cattle (Abdelaziz et al., 2024; Mingxiao et al., 2006). This variability highlights the complexity of translating immunological findings across species during vaccine development.

In food-producing animals, ethical and regulatory constraints further complicate vaccine use, particularly in ensuring consumer safety. Vaccines administered to livestock such as pigs or cattle must undergo rigorous evaluation to confirm the absence of harmful residues in meat, milk, or eggs. Regulatory frameworks also mandate clearly defined withdrawal periods following vaccination to prevent vaccine components from entering the human food chain. These requirements pose unique challenges in balancing effective immunization with food safety standards. Furthermore, ethical and regulatory considerations

impact the use of genetically modified organisms (GMOs) and long-lived vaccine vectors such as recombinant spores, due to potential environmental concerns. These factors can limit regulatory approval and public acceptance despite the scientific promise of such technologies (Hoelzer et al., 2018).

Similarly, in companion animals such as dogs and cats, ethical considerations influence vaccination strategies, particularly regarding repeated or lifelong immunization schedules. The potential for adverse reactions necessitates careful assessment of the frequency and necessity of booster vaccinations. Regulatory oversight aims to optimize disease protection while minimizing risks to animal welfare, ensuring that vaccination protocols are both safe and justified.

Also, the choice of vaccine delivery route depends on species-specific anatomy, immune responses, and practical constraints. While mucosal routes such as oral or nasal delivery are suitable for targeting the entry points of many pathogens, mucosal immunity varies between species and is often compartmentalized. Oral delivery is particularly suitable for mass vaccination in poultry and wildlife, although bait formulations and baiting strategies must be tailored to the target species. Automated in ovo vaccination is an emerging approach in poultry, whereas intramuscular injection remains an effective vaccine delivery route in fish. For DNA vaccines, advanced delivery approaches such as biolistic particle delivery using a gene gun and electroporation have been investigated to improve transfection efficiency. Gene-gun delivery introduces DNA into target tissues through biolistic particle bombardment, whereas electroporation applies brief electrical pulses to enhance cellular uptake of the administered DNA by transiently increasing cell membrane permeability. Although these approaches may improve DNA vaccine delivery, they are not yet routinely used in livestock and largely remain at the research stage (Chambers et al., 2016).

Additionally, epidemiological differences and husbandry practices further complicate vaccine regulation across species. For example, aquaculture species require vaccination methods adapted to their aquatic environment, such as immersion or oral delivery, which differ markedly from the injectable vaccines commonly used in terrestrial animals (Embregts and Forlenza, 2016). These logistical and biological challenges demand specialized regulatory pathways to ensure that vaccines are effective within their specific contexts.

Although the cost of monoclonal antibody (mAb)-based treatments remains prohibitive for widespread use in food-producing species, large animal models and the development of species-specific reagents are playing an increasingly important role in evaluating the manufacture, delivery, and efficacy of such biologics under the One Health framework. The growing availability of genomic information and the use of alternative expression systems such as *Pichia pastoris*, insect, and mammalian cells have expanded access to species-specific immune proteins. The yeast *P. pastoris* expression system is one of the most popular and standard tools for the production of recombinant protein in molecular biology (Karbalaie et al., 2020).

The veterinary immunology community has a longstanding tradition of collaborative progress through initiatives such as the HLDA (Human Leukocyte Differentiation Antigens) workshops, international CD (Cluster of Differentiation) workshops, immunological toolbox programs, toolkit committees, and collective funding mechanisms. These coordinated efforts have significantly enhanced the development and availability of reagents tailored to different species, thereby facilitating more precise and effective vaccine strategies (Entrican et al., 2020).

Comparison with human vaccine regulatory pathways: While veterinary and human vaccine regulatory frameworks share the common goals of ensuring safety, efficacy, and quality, there are distinct differences reflecting the unique contexts of each field (Table 3).

Human vaccine regulations are often more standardized globally, with well-established pathways and harmonized guidelines driven by agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO). These agencies have well-established clinical trial structures, including clearly defined Phase I, II, and III studies, and consistent Good Manufacturing Practice (GMP) expectations across regions. In contrast, veterinary vaccine regulation must accommodate a broad and diverse range of target species, each with unique physiological, immunological, and metabolic characteristics (Francis, 2020). This diversity, coupled with variations in disease epidemiology and animal husbandry practices, necessitates species-specific study designs and results in more heterogeneous regulatory requirements across countries (Knight-Jones et al., 2014). Unlike the human vaccine process, the veterinary approach relies heavily on real-world field trials to establish effectiveness and safety in the actual target species (Francis, 2020).

Additionally, veterinary vaccine pathways often incorporate considerations for environmental impact and food safety such as environmental impact, shedding and spread of live vaccines (especially of exotic serotypes), reversion to virulence, and the presence of vaccine residues in animal-derived products due to the direct connection between animal health and human food supply. As a result, veterinary regulatory frameworks incorporate food safety principles through mandated withdrawal periods and residue testing, ensuring public health protection through the food chain (Chambers et al., 2016). Adjuvant use in veterinary vaccines also tends to be more flexible, with a broader range of permitted substances tailored to different species, unlike the strictly regulated adjuvant profiles of years-long phase studies for human vaccines (Del Giudice et al., 2018). Post-marketing surveillance in veterinary medicine is generally less formalized and more variable across regions compared to the highly structured systems used in human health. Nevertheless, it remains an important component in ensuring ongoing safety and efficacy (Fathelrahman, 2020). Regulatory timelines in veterinary medicine may also be more flexible to allow rapid responses to emerging animal disease outbreaks.

However, the lack of global harmonization in veterinary vaccine regulation can complicate multinational licensure efforts (Badshah *et al.*, 2024). Together, these differences necessitate tailored,

species-specific regulatory approaches in veterinary medicine while maintaining alignment with the core principles of product safety, efficacy, and quality seen in human vaccine development.

Table 3 Comparison of veterinary and human vaccine regulatory pathways.

Aspect	Veterinary Vaccines	Human Vaccines
Regulatory Authorities	• Less global harmonization	• Globally standardized and harmonized pathways
Target Population	• Broad range of species (livestock, companion, wildlife) • Species-specific immune and physiological differences	• Humans only • Relatively uniform physiology across population
Disease context and Epidemiology	• Varies widely by species, region, and farming practices. • Some diseases affect multiple species, others are species-specific, both types can be zoonotic	• Focuses on diseases that affect human populations, with global surveillance and more uniform patterns.
Clinical Trial	• No formal Phases I-III • Uses target species studies and field trials	• Standardized Phases I, II, III trials in humans
Efficacy Testing	• Conducted in natural hosts under real-world or field conditions	• Conducted under controlled settings in human volunteers
Safety Evaluation	• Assesses shedding, reversion to virulence (live vaccines), environmental safety, food residue	• Assesses human toxicity, adverse events, and pharmacokinetics
Environmental & Food Safety	• Strong emphasis; includes withdrawal periods and residue testing in products that are for human use / consumption	• Less direct concern; primarily public health-driven
Adjuvant	• Broader range permitted • Highly varied across species and products	• Tightly regulated • Requires extensive safety validation
Good Manufacturing Practice (GMP)	• Required, but standards may vary regionally and by species	• Strict GMP compliance with uniform global expectations
Regulatory timelines	• Often shorter and more flexible, especially for outbreaks in animals. • Timelines vary by country.	• Usually longer, with fixed phases (I-III), and strict global regulations. • Emergency approvals are possible but rare.
Post-Marketing Surveillance	• Less centralized • Varies by region and species	• Mandatory, centralized pharmacovigilance systems

Emergency approval processes of veterinary vaccines: Emergency vaccination campaigns, including their therapeutic application, play a vital role in controlling disease outbreaks caused by the introduction of infectious agents into susceptible populations, where there is a risk of rapid transmission, severe clinical consequences, and/or substantial economic losses. These campaigns are crucial for containing outbreaks of vaccine-preventable diseases (VPDs), reducing the likelihood of international spread and sanctions, and thereby strengthening global health security (Walldorf *et al.*, 2017). In situations where non-vaccination policies are deemed unacceptable, economically burdensome (like large-scale culling), or ineffective, emergency vaccination provides a critical alternative or complement to routine prophylactic measures. This approach is particularly relevant for re-emerging diseases or in regions with sporadic outbreaks, such as foot-and-mouth disease (FMD) and classical swine fever (CSF).

For example, during an FMD outbreak, the UK enforced standard EU measures including culling and movement restrictions, whereas the Netherlands adopted a more integrated approach by combining these with emergency vaccination of livestock in the affected zones, followed by culling of vaccinated animals. These differing strategies highlight how emergency vaccination -where it is scientifically proven to be useful and recommended- can be flexibly

adapted based on national contexts and policy preferences (Orsel and Bouma, 2009).

To be effective, veterinary emergency vaccination must be tailored to the specific disease, rapidly deployed based on real-time epidemiological data, and supported by surveillance systems, robust biosecurity, and readily accessible vaccine stockpiles (Metwally *et al.*, 2021). High immunization coverage is essential, alongside strict controls on the movement of potentially infected animals outside vaccinated zones (FAO). Biosecurity measures must also be enforced to ensure that vaccination teams do not inadvertently facilitate disease transmission. Moreover, diverse emergency vaccination strategies ranging from ring vaccination to suppressive or protective approaches should be adapted to the outbreak dynamics (Kahn *et al.*, 2002).

Despite its benefits, emergency vaccination campaigns face significant logistical and regulatory challenges. These include forecasting vaccine demand, securing sufficient supplies during global shortages, and overcoming regulatory hurdles for the timely deployment of new or updated products. Consequently, national veterinary services must develop rapid response capabilities for disease emergencies, whether triggered by natural disasters, trade disruptions, or re-emerging infections. Integrating emergency vaccination into national contingency plans is crucial, as it enhances animal health resilience, mitigates economic losses, and supports safe international trade by reducing the risk

of transboundary disease spread (Walldorf *et al.*, 2017;; WOA, 2025).

To support rapid deployment during emergencies, regulatory frameworks must provide mechanisms for expedited vaccine approval. Emergency veterinary vaccination policies should be embedded within a broader framework of legal, trade, and regulatory considerations. Existing legislation often requires revision to facilitate the use of emergency vaccination and to address constraints related to veterinary product approvals and international trade of products derived from vaccinated animals (OIE WOA, 2014).

The World Organisation for Animal Health (WOAH) Terrestrial Code offers general guidance on vaccination programmes (Chapter 4.18) and official control measures for listed and emerging diseases (Chapter 4.19) but lacks specific provisions for emergency vaccine registration. Nevertheless, some agencies can issue rapid authorizations for non-routinely used vaccines in response to disease emergence or introduction risks. Such pathways often involve reduced data requirements, accelerated reviews, and restrictions based on region, time, or animal population. A notable example of emergency approval is the emergency approval of vaccines for serotype-3 bluetongue virus in Europe, where existing vaccines were ineffective against the new strain (Baptiste Dungu and García-Campos, 2025).

One structured example for vaccination policy during emergency animal disease responses is the Australian Veterinary Emergency Plan (AUSVETPLAN, 2007), which classifies vaccine use into four tiers: Primary: vaccination alone or with stamping-out, Secondary: supports stamping-out, Tertiary: used in prolonged or entrenched outbreaks, Non-use: in cases of safety concerns, trade issues, or lack of vaccine availability.

These categories allow for dynamic decision-making based on outbreak circumstances and policy objectives. While Australia's policy for certain diseases, such as classical swine fever, traditionally favors stamping-out over vaccination, other countries with endemic challenges may adopt vaccination as a primary strategy. This classification underscores the importance of pre-outbreak scenario planning and policy readiness to facilitate rapid, effective responses tailored to disease characteristics and national priorities (Australia, 2005).

With the global push toward disease eradication, rising public resistance to mass culling, and concerns about antimicrobial overuse, emergency vaccination is increasingly favored as a humane and sustainable disease control strategy (Miguel *et al.*, 2020). Its use is particularly justified in high-density animal populations, during multifocal outbreaks where early detection has failed (as exemplified by the spread of porcine epidemic diarrhea virus in the United States), airborne pathogen scenarios, or deliberate biological threats (FAO; Sajjadi *et al.*, 2025; Williams, 2007).

The success of emergency vaccination efforts depends not only on the rapid deployment of vaccines but also on the availability of advanced diagnostic tools. These tools are essential for confirming the absence of pathogens in vaccinated animals and their products, thereby facilitating safe trade and

maintaining market access. There is growing support for the 'vaccinate to live' strategy, which promotes allowing vaccinated animals to complete their natural production cycle instead of being culled prematurely. To enable this approach, it is crucial to establish and maintain vaccine and diagnostic banks during disease-free periods, ensuring swift and effective responses when outbreaks occur (WOAH, 2025).

Key Data Requirements in Veterinary Vaccine Registration

Veterinary vaccine registration mandates a structured, evidence-based data package to ensure the product's safety, efficacy, and quality before market entry. Regulatory authorities require extensive documentation and validated study results to ascertain a vaccine's suitability for use in diverse animal populations under real-world conditions. The following components represent the cornerstone data categories in the regulatory dossier.

Preclinical evaluation: Preclinical studies serve as the crux of regulatory submissions by establishing fundamental safety and immunogenicity profiles, which are essential for advancing to late-phase specifications and transitioning the vaccine from the laboratory to the target species (Limpikirati *et al.*, 2024).

Initial assessments are often conducted in laboratory animal models (e.g., mice, guinea pigs) to evaluate preliminary safety and immune responses. However, due to species-specific differences in immune systems, bridging studies in target species such as swine, poultry, or cattle are typically required to validate the relevance and translatability of these findings (WOAH, 2018).

Dose-ranging studies are conducted to identify the optimal antigen dose that induces a strong immune response with minimal adverse effects. These studies help define the minimum effective dose and the maximum tolerated dose, ensuring efficacy while minimizing the risk of toxicity (Tanner and Morgan, 1993).

Determining the safety margin is another critical component, assessing how much higher a dose can be administered without causing harm. This information supports the development of label instructions and helps account for potential dosing inaccuracies under field conditions (Gifford *et al.*, 2011; Thomas *et al.*, 2022).

Efficacy trials in target animals: Efficacy trials in target animals are a core requirement for veterinary vaccine registration, as they provide direct evidence that the vaccine performs as intended under controlled and field conditions. These studies are designed to demonstrate the vaccine's ability to stimulate a protective immune response and to reduce infection, clinical disease, or transmission in the intended species (Additives and Feed, 2011).

Conducted in real-world settings, field trials aim to assess vaccine performance under typical farm or production conditions. In the EU, the requirement for field efficacy data in support of veterinary vaccine marketing authorisation is established under Directive

2001/82/EC. This directive mandates that laboratory efficacy studies be complemented by field trials unless a valid justification for their omission is provided. The primary aim of these trials is to demonstrate a vaccine's effectiveness under practical, real-world conditions, ideally involving natural exposure to the target pathogen. The Committee for Medicinal Products for Veterinary Use (CVMP) provides further guidance through its field study guidelines, supported by the European Pharmacopoeia Monograph 5.2.7. However, industry stakeholders, as highlighted in a 2017 EMA/HMA focus group meeting, have questioned the cost-effectiveness of these studies, particularly in cases where natural pathogen challenge does not occur during the trial period. The regulatory landscape has evolved with the introduction of Regulation (EU) 2019/6, which came into effect in 2022. This regulation introduces greater flexibility by allowing exemptions from field efficacy requirements for certain vaccine types or indications. In response, the CVMP released a concept paper in 2021 proposing updates to existing guidelines on field trials and vaccine indications (Mackay *et al.*, 2021).

Challenge models involve the intentional exposure of vaccinated and control animals to a virulent strain of the pathogen. These studies are typically performed under controlled laboratory or containment conditions to directly measure the vaccine's protective efficacy. Outcomes may include prevention of infection, reduction in clinical signs, or limitation of pathogen shedding. While early-stage studies often use rodents like mice or guinea pigs, their immune systems and infection profiles frequently differ from natural hosts, limiting the relevance of results. Transgenic rodents can improve permissiveness but may still fail to replicate the full pathogenesis of disease. In contrast, using the natural host species such as cattle, pigs, or sheep provides more accurate and regulatory-relevant data. These models enable assessment of critical factors such as virus shedding, carrier status, immune response, and clinical protection that cannot be reliably evaluated in rodent models (Cosby, 2024).

Immunological endpoints such as antibody titres, virus neutralization, cytokine levels, or cell-mediated immune responses are also evaluated to characterize the immune response elicited by the vaccine. While these markers provide important correlates of protection, they must be validated against clinical or challenge outcomes to confirm their relevance. Since vaccines are comprised of multiple components, multiple immunological endpoints are used to identify the least effective vaccine components (Hörig and Pullman, 2004).

Safety and tolerance studies: Safety and tolerance studies are critical to support the clinical development and regulatory approval of veterinary vaccines. These studies evaluate both local and systemic reactions to ensure that post-vaccination effects remain within acceptable limits across diverse animal populations. Vaccine-related toxicity can stem either from the intrinsic properties of the constituent materials leading to injection site or systemic reactions, or from the pharmacodynamic action of the vaccine, such as immune-mediated effects (Gifford *et al.*, 2011).

Local tolerance studies assess tissue responses at the injection site through gross pathology and histopathological evaluation, helping differentiate between expected inflammatory responses and adverse pathological changes. Single-dose toxicity studies provide preliminary data on acute tolerability and are especially important for vaccines containing antigens with intrinsic pharmacological activity or when assessing the effects of potential overdose (Pilling *et al.*, 2002).

Repeated-dose toxicity studies are the cornerstone of vaccine safety evaluation. These studies assess the cumulative effects of multiple administrations, including reactogenicity, live vaccine attenuation, and persistent immune responses. Conducted at multiple time points, they help identify both immediate and long-term adverse effects, supporting the safety of the full dosing schedule (Forster, 2012).

Reproductive and developmental safety studies evaluate potential effects on fertility, gestation, and offspring in breeding animals to ensure that the vaccine does not interfere with reproductive performance (Barrow, 2000). Safety pharmacology studies, conducted only when warranted, investigate potential off-target effects on vital physiological systems (Pugsley *et al.*, 2008).

In addition, as an extension from human to animal studies, safety must be demonstrated in special populations including young, aged, pregnant, or immunocompromised animals to confirm that the vaccine is suitable for all intended use groups under field conditions (Doherty *et al.*, 2016).

Chemistry, Manufacturing and Controls (CMC): A critical component of veterinary vaccine registration is the submission of detailed Chemistry, Manufacturing, and Controls (CMC) data, which encompasses quality-related aspects of vaccine product development, including the characterization of relevant physicochemical and biological properties, manufacturing processes, and quality control strategies. The quality, identity, purity, potency, and strength of both the vaccine antigen or active component and the finished vaccine product are critical to ensuring that the product performs as intended. These factors directly impact the vaccine's performance and reliability in the field. The extent of CMC activities varies depending on the complexity of the vaccine product, its formulation, and the stage of development (DiFeo, 2004). CMC requirements do vary between human and animal products, reflecting differences in regulatory frameworks, intended use, and safety considerations.

A thorough Chemistry, Manufacturing, and Controls (CMC) evaluation is a critical component of veterinary vaccine registration, ensuring that each product is consistently safe, effective, and of high quality. Regulatory authorities require detailed, scientifically justified documentation covering formulation development, manufacturing processes, quality control, packaging, and stability supported by validated analytical methods and real-world data. The scope of CMC data depends on the vaccine's molecular complexity (e.g., live attenuated, inactivated, recombinant), formulation, and development stage.

Veterinary-specific requirements may also differ from human vaccines due to variations in intended use and species-specific safety considerations. Quality control strategies must demonstrate batch-to-batch consistency in key parameters such as purity, potency, sterility, and stability, confirmed through robust

validation and characterization studies (Barrett, 2022). Table 4 provides a consolidated checklist of key CMC review aspects relevant to veterinary vaccines, adapted from established pharmaceutical regulatory standards, with emphasis on antigen stability, reproducibility, and overall product integrity (DiFeo, 2003).

Table 4 Checklist of key CMC review aspects.

Category	Key Review Aspects	Inference for Veterinary Vaccines
Formulation and Excipient Compatibility	- pH stability - Vaccine component-excipient interaction (liquid/solid forms) - Thermal stability - Buffering agents - Aggregation potential - Effect of oxygen - Cosolvents - Preservative systems	Ensures vaccine antigen integrity and stability, particularly in multi-dose, adjuvanted, or thermolabile formulations.
Suspension and Lyophilized Product Attributes	- Sedimentation and resuspendibility - Particle size distribution - Homogeneity - Freeze-drying parameters - Diluent compatibility	Critical for consistent dosing, reconstitution quality, and field applicability.
Excipient Quality Attributes	- Moisture content - Polymorphism (crystallinity) - Flowability - Surface area and particle shape - Residual solvents - Impurity profile	Supports consistent manufacturing, product uniformity, and interaction-free formulation.
Manufacturing Process Development	- Defined CQAs and CPPs - Scale-up feasibility - Rework frequency - Filter compatibility (liquids) - Process validation (3 batches) - Cleaning validation	Ensures reproducible large-scale production with controlled process variability.
Container Closure System (Packaging)	- Primary package compatibility - Sterility and integrity - Light and oxygen protection - Qualification data	Vital for ensuring vaccine stability and potency over shelf life under varied storage conditions.
Vaccine Product Microbiological Attributes	- Sterility for parenteral vaccines - Endotoxin control - Environmental monitoring	Mandatory for injectable vaccines to meet safety standards.
Analytical Methods and Control Strategy	- Validated methods for identity, potency, purity - Assay precision, linearity, robustness - Control of impurities and residuals	Confirms batch quality, consistency, and alignment with regulatory specifications.
Batch Analysis and Process Validation	- Data from developmental and full-scale batches - Process flow diagrams - Impurity reproducibility - Acceptance criteria for intermediates	Demonstrates manufacturing consistency and robustness prior to market release.
Stability Testing	- Real-time and accelerated studies - Degradation profiling - Shelf-life justification - In-use stability (multi-dose vials)	Establishes appropriate storage conditions, expiration date, and label claims.

*CMC, Chemistry, Manufacturing, and Controls; CQA(s), Critical Quality Attribute(s); CPP(s) Critical Process Parameter(s).

Labelling, pharmacovigilance, and post-market surveillance: Labelling plays a central role in guiding veterinarians and animal health professionals on the correct use of a vaccine. Regulatory agencies require that labels include comprehensive and accurate information such as the product name, target species, dosage, route of administration, withdrawal periods for food-producing animals, storage conditions, and expiry dates, in the required (local) language. Label content must be based on data submitted during the

pre-licensing phase and is subject to review and approval to prevent off-label use or misuse that could compromise vaccine performance or animal safety (van der Riet, 2021).

Pharmacovigilance involves the continuous collection, evaluation, and reporting of adverse events related to licensed veterinary vaccines. Regulatory authorities generally require manufacturers to implement robust adverse event monitoring systems and to submit periodic safety update reports (PSURs).

However, under Regulation (EU) 2019/6, which became applicable on 28 January 2022, periodic safety update reports (PSURs) are no longer required for veterinary medicinal products in the European Union. Instead, marketing authorisation holders are required to undertake continuous pharmacovigilance and signal management activities to monitor the benefit-risk balance of authorised veterinary products throughout their lifecycle.

Where required, PSURs provide comprehensive assessments of a vaccine's risk-benefit profile at specified intervals following authorization. Through PSUR evaluations, regulators can determine whether additional investigations are warranted or if regulatory actions are needed to safeguard animal and public health. Pharmacovigilance systems are essential for detecting rare or delayed adverse effects, potential interactions with other veterinary products, and species-specific sensitivities that may not have been fully identified during pre-approval studies. In many regions, adverse event reports must be submitted within strict deadlines and can prompt further inquiry or enforcement measures by regulatory bodies (EMA, 2013).

Post-market surveillance (PMS) complements pharmacovigilance by assessing a vaccine's real-world effectiveness and field safety across broader populations and varying environmental conditions. Surveillance activities may include field studies, batch consistency evaluations, epidemiological monitoring, and sampling of marketed products to confirm potency and sterility. In the case of adverse findings, regulators may initiate batch recalls, update product labels, impose restrictions, or in rare cases, revoke product licenses (Gifford et al., 2011).

Global Regulatory Frameworks for Veterinary Vaccines

Regulatory authorities worldwide have implemented various mechanisms to support the emergency approval and oversight of veterinary vaccines, particularly in the context of transboundary animal diseases (TADs) and emerging infectious threats. These frameworks vary in structure and scope but aim to strike a balance between rapid access and assurance of safety and efficacy. The following sections outline key international and national regulatory systems including those established by the WOAHA (formerly OIE), the USDA-APHIS, the European Medicines Agency (EMA) and ASEAN highlighting their roles, principles, and collaborative efforts specific to veterinary vaccine development and deployment (Table 5).

World Organisation for Animal Health (WOAH/OIE): The World Organisation for Animal Health (WOAH), founded in 1924 as the Office International des Epizooties (OIE) and adopting its current name in May 2003, is an intergovernmental organization recognized as the global authority on animal health. The World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) formally recognizes as the international standard-setting organization for animal

health and zoonoses. Its primary focus is on transparently disseminating information on animal diseases, improving animal health globally, and thus building a safer, healthier, and more sustainable world. WOAHA's role at the international level includes supporting the controlled deployment of emergency vaccines, especially for transboundary animal diseases. It provides crucial guidance to ensure that vaccines used under such conditions meet required standards of quality, safety, and efficacy, thereby safeguarding both animal and public health (WOAH, 2025).

The WOAHA plays a critical role in global animal health through its Terrestrial Animal Health Code (Terrestrial Code) (WOAH, 2024a, 2024b). This comprehensive document establishes standards aimed at improving animal health, animal welfare, and veterinary public health globally. These standards guide WOAHA Members in developing measures for the prevention, early detection, reporting, and control of pathogenic agents in terrestrial animals (mammals, reptiles, birds, and bees), including zoonotic agents. Adherence to the Terrestrial Code's recommendations is vital for ensuring the safety of international trade in animals and animal products, while simultaneously preventing unjustified sanitary barriers (Asokan, 2025).

To uphold this framework, WOAHA Members are obliged to report detailed information about their animal health status, encompassing both domestic and, where relevant, wild animal populations. This reporting aligns with the mandates of both the Terrestrial Animal Health Code and the Aquatic Animal Health Code. This commitment serves two main purposes: it facilitates the exchange of information on "listed diseases" (those prioritized by WOAHA Members) and enables the rapid sharing of data on unusual animal health incidents, whether they involve listed diseases or newly emerging threats. To maintain country participation, the criteria for prioritizing diseases, the list of these diseases, and the scope of early information sharing are subject to review and adoption through Member voting. However, a significant hurdle for global surveillance systems is that some listed diseases occurring in wild animals do not meet the Terrestrial Code's strict definition, meaning their notification isn't always mandatory. Standardizing and coordinating this data collection remains a key challenge for effective global surveillance (Thompson et al., 2024).

The responsibility for crafting and updating the Terrestrial Code's standards rests with the Terrestrial Animal Health Standards Commission (the Code Commission), a body composed of six elected members. This Commission taps into the knowledge of globally recognized experts to ensure that all standards are continually grounded in the latest scientific advancements. To gather diverse perspectives and build consensus, new or revised texts are circulated twice annually for comments from Members and partner international organizations. The Code Commission also collaborates closely with WOAHA's other specialized commissions (WOAH, 2024b).

European Medicines Agency (EMA): The European Medicines Agency (EMA) is a decentralized regulatory

body of the European Union entrusted with the scientific evaluation, supervision, and safety monitoring of medicines for both human and veterinary use. EMA's Committee for Medicinal products for Human Use (CHMP) or Committee for Medicinal products for Veterinary Use (CVMP) carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not. Established in 1995, the EMA plays a central role in ensuring that all pharmaceuticals authorized within the EU meet the highest standards of quality, safety, and efficacy. Operating through a coordinated network of scientific committees and national regulatory authorities, the agency provides a robust framework for assessing medicinal products throughout their life cycle. EMA's core objectives include promoting public and animal health by fostering innovation, providing scientific and regulatory guidance, and supporting the harmonization of pharmaceutical regulations across member states (Kamiseti, 2023). Within the European Union, the European Medicines Agency (EMA), through its Committee for Veterinary Medicinal Products (CVMP), can issue emergency marketing authorizations under accelerated assessment procedures. These are granted under exceptional circumstances, enabling rapid vaccine deployment during animal health crises. The agency is committed to transparency and scientific rigor, offering early support to pharmaceutical developers, particularly in emerging fields such as advanced therapy medicinal products (ATMPs). Through its procedures and guidance, EMA not only strengthens the EU's internal regulatory landscape but also contributes to shaping global standards in medicine development and oversight (Grein, 2009).

EMA coordinates a centralised procedure, which is a regulatory pathway that enables a single marketing authorisation to be valid across all EU Member States, as well as in Iceland, Liechtenstein, and Norway. This approach streamlines the authorisation of veterinary medicinal products by allowing one application, one evaluation, and one decision applicable throughout the European Economic Area (EEA) (Faden and Kaitin, 2008).

Key features of the centralised procedure include eligibility, single assessment timeline, final authorization, consistency and accelerated and conditional approval (EMA, 2019). Eligibility for the centralised procedure is typically mandatory for certain categories of products. Certain products, such as those involving biotechnology, gene therapies, orphan drugs, and vaccines for high-impact diseases (e.g., cancer, HIV, diabetes) and veterinary medicines for use as growth or yield enhancers are required to mandatorily undergo the centralised procedure. Other products may apply this pathway voluntarily, especially if they represent a major therapeutic innovation or contribute to public interest at the European level (Bharath *et al.*, 2019).

Once accepted into the centralised procedure, products undergo a single assessment timeline coordinated by the Committee for Medicinal Products for Veterinary Use (CVMP) or Committee for Medicinal products for Human Use (CHMP). This

timeline spans approximately 210 active days and includes scheduled pauses or "clock-stops" to allow the applicant to respond to questions or provide supplementary data. The CVMP conducts a rigorous scientific review during this period, evaluating the quality, safety, and efficacy of the product in question (EMA, 2019).

In case of the marketing authorisation of veterinary medicines, before the scientific evaluation begins, applicants must complete several preparatory steps that ensure regulatory alignment and procedural clarity. These include submitting an eligibility request to confirm that the product qualifies for the centralised route, followed by a formal notification of intent to submit a marketing authorisation application. The EMA then appoints (co-)rapporteurs from the relevant scientific committees to lead the assessment. Applicants are also encouraged to engage in pre-submission meetings with the EMA, which serve to clarify procedural expectations, address potential data gaps, and improve dossier quality, ultimately facilitating a smoother validation and review process (EMA, 2015a). Once the application is submitted, EMA performs a validation check to confirm completeness before initiating the formal evaluation timeline. Following this evaluation, a final opinion is issued by the CVMP and forwarded to the European Commission. The Commission typically issues a legally binding marketing authorisation within 67 days of receiving the CVMP's recommendation. This authorisation is automatically valid in all EU/EEA countries, eliminating the need for separate national applications and ensuring a harmonised product launch (EMA, 2019).

One of the most important strengths of this procedure is the consistency it provides in regulatory outcomes. The product's labelling, package leaflet, and summary of product characteristics (SPC) are uniformly approved across all jurisdictions, ensuring coherent and transparent communication for veterinarians, manufacturers, and regulatory bodies alike (EMA, 2015a; 2019; 2026b).

Additionally, the centralised procedure includes options for accelerated and conditional approvals. Accelerated assessment shortens the standard evaluation period for a marketing authorisation application, allowing CVMP to complete its review more quickly. This pathway is available when the CVMP considers the product to be of significant importance for public health and therapeutic innovation. While a typical evaluation under the centralised procedure may take up to 210 active days (excluding clock-stops for applicant responses), the CVMP can reduce this timeframe to 150 days upon request, provided the applicant offers a well-substantiated justification for expedited review (EMA, 2015b). In urgent public or animal health scenarios, applicants may receive a conditional marketing authorisation, allowing earlier access to the market based on preliminary but promising data. Accelerated assessment reduces the timeframe for the CVMP to review a marketing-authorisation application. Similarly, approvals under exceptional circumstances may be granted when comprehensive data collection is

not feasible, such as in the case of rare diseases or ethical limitations on trial designs (EMA, 2015b; 2016).

United States – USDA (APHIS, CVB): In the United States, the regulation of veterinary vaccines is overseen by the U.S. Department of Agriculture (USDA), through the Animal and Plant Health Inspection Service (APHIS) and its dedicated unit, the Center for Veterinary Biologics (CVB). The regulation of veterinary drugs is entrusted to the Center for Veterinary Medicines (CVM), which is a FDA Center. The legal basis for this regulatory oversight stems from the Virus-Serum-Toxin Act of 1913, which governs the production, importation, sale, and distribution of veterinary biological products including vaccines, bacterins, antisera, diagnostic kits, and recombinant products ensuring that they are safe, pure, potent, and effective before they reach the market (Elsken *et al.*, 2007).

The licensing of veterinary vaccines in the United States is governed by the regulations specified in Title 9 of the Code of Federal Regulations (CFR), Parts 101–118. These regulations outline the complete data requirements for securing a conventional product license or a permit for distribution and sale. The CVB evaluates all pre-licensing data to ensure that each product meets the required standards for purity, safety, potency, and effectiveness. The product licensing process requires detailed submissions on master seed and cell characterization, manufacturing methods, purity, safety, potency, stability, and efficacy which is typically demonstrated through vaccination-challenge and field safety studies. Purity standards mandate the exclusion of extraneous microorganisms, and safety studies may include environmental and reproductive safety, especially for live vaccines and adjuvanted products (Elsken *et al.*, 2007).

The CVB uses a risk-based approach to assess conventional and biotechnology-derived products, guided by Summary Information Formats (SIFs) and risk assessments. These formats differ based on product type such as conventionally-derived live vaccines or Category I, II, and III biotechnology-derived vaccines, which include inactivated products, gene-deleted live vaccines, and live vector vaccines, respectively. In addition to product-specific risks, the USDA also evaluates potential environmental impacts associated with the release of new live vaccines (Service, 2024).

Besides conventional product licenses, the USDA offers other licensing options to meet specific needs. Special license types include conditional licenses for emerging disease threats, and autogenous licenses for herd-specific vaccines. The USDA also issues import permits, with the full permit for distribution equating to a domestic product license. For the importation of veterinary biologics into the U.S., the USDA issues three types of permits: for transit shipment only, for research and evaluation, and for distribution and sale.

The last type is equivalent to a full veterinary biological product license and is subject to the same regulatory scrutiny as domestically produced vaccines (Erdman *et al.*, 2020).

All manufacturers of veterinary biologics intended for distribution in the United States must obtain a Veterinary Biologics Establishment License, with foreign manufacturers required to partner with a U.S.-based permit holder. Before licensure, the Center for Veterinary Biologics (CVB) conducts thorough pre-licensing inspections to assess facility design, biosafety protocols, equipment, sanitation practices, and personnel qualifications. These inspections are structured across 14 categories, covering licensing conditions, research activities, seed and cell line management, production processes, quality control, labeling, distribution, and the use of animals in testing. A key component of the licensing process is confirmatory testing conducted by the CVB laboratory, which independently evaluates biological seeds, cell substrates, and final product batches to verify purity, safety, and potency. Post-licensure, manufacturers remain under ongoing oversight through unannounced inspections, mandatory record-keeping, and post-marketing surveillance programs. The CVB also requires submission of representative samples from each batch, and only those that meet all regulatory standards are approved for commercial release (Elsken *et al.*, 2007).

ASEAN regions: The Association of Southeast Asian Nations (ASEAN) is actively pursuing regulatory convergence for veterinary vaccines through the adoption of the ASEAN Common Technical Dossier (ACTD) for Veterinary Products (Godiyal, 2019). The ACTD provides a standardized format to streamline submission and evaluation processes across member states, facilitating more efficient and harmonized regulatory reviews. Although originally developed for pharmaceuticals for human use, particularly in Part II: Quality - covers biologics, including biotechnological products and vaccines. The ACTD's framework demonstrates a shared regional approach to ensuring the quality of complex products such as vaccines. It outlines detailed requirements for both drug substances and finished products, including manufacturing processes, characterization, quality control, analytical procedures, and stability data, with references to WHO guidelines for variations (ASEAN). This harmonized system reflects ASEAN's broader objective of establishing mutual recognition and alignment of regulatory procedures by 2025, aiming to reduce redundancy and accelerate market access. Modelled in part after the European Medicines Agency (EMA), the ASEAN framework underscores regional cooperation and adherence to international standards, fostering innovation while enhancing animal health and facilitating intra-regional trade (ASEAN, 2012).

Table 5 Comparative analysis of timelines, dossier requirements, and review processes.

Regulatory Body	Timeline to Approval	Dossier Requirements	Review Process Characteristics
EMA (EU)	~210 active days for CVMP scientific opinion + 67 days for European Commission decision	Full Common Technical Document (CTD) with eAF, multi-lingual SPC, GMP compliance, quality/safety/efficacy modules, and pharmacovigilance plan	Centralised evaluation by the CVMP; single EU-wide authorisation; clock-stops allowed; allows conditional and accelerated approvals
USDA (APHIS-CVB, USA)	Varies; conditional license possible within months; full license upon complete data	Hard copy dossier including manufacturing protocols, safety, efficacy, purity, potency, field safety data, serial release protocols	Scientific review by CVB specialists; conditional licenses permitted for emergency needs; continued data required post-approval
ASEAN Region (Harmonisation initiative)	No unified system yet; harmonisation underway; mutual recognition goal by 2025	ASEAN Common Technical Dossier (ACTD for Veterinary) under development; aligned with VICH-GFI structure; aims for unified format	Regional collaboration through ASEAN Pharmaceutical Regulatory Framework (APRF); building capacity for harmonised review and mutual recognition.

* ACTD, ASEAN Common Technical Dossier; APHIS, Animal and Plant Health Inspection Service; APRF, ASEAN Pharmaceutical Regulatory Framework; ASEAN, Association of Southeast Asian Nations; CTD, Common Technical Document; CVB, Center for Veterinary Biologics; CVMP, Committee for Veterinary Medicinal Products; eAF, electronic Application Form; EMA, European Medicines Agency; EU, European Union; GFI, Guidance for Industry; GMP, Good Manufacturing Practice; SPC, Summary of Product Characteristics; USDA, United States Department of Agriculture; USA, United States of America; VICH, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

Regional Harmonization and International Collaboration

Regional harmonization and international collaboration are critical components of veterinary regulatory frameworks, enabling alignment of technical requirements, mutual recognition of data, and coordinated responses to emerging and transboundary animal diseases. This section outlines key international efforts to standardize regulatory practices, emphasizing the role of global organizations, region-specific harmonization strategies, pivotal guidelines, and cross-sectoral collaborations that collectively support efficient vaccine development, safety monitoring, and global health preparedness.

Role of VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is a multinational program established in April 1996 that functions to promote unified technical guidelines for the registration of veterinary medicinal products across major global regions (Research, 2011). The acronym VICH originates from its earlier name, "Veterinary International Conference on Harmonisation," which was retained for continuity despite the official name change. Formed as a trilateral initiative involving the European Union, Japan, and the United States, and later expanded to include observer countries and regional representatives, VICH aims to reduce duplication of testing, facilitate mutual recognition of data, and streamline the regulatory approval process (FDA, 2024).

The WOAHP (previously known as OIE) played a foundational role in the creation of VICH and continues to contribute actively through its participation in the VICH Steering Committee. WOAHP provides essential guidance and helps promote the dissemination of VICH's harmonized guidelines. Leveraging its extensive network of 183 Member Countries, WOAHP supports the global exchange of these standardized technical requirements, fostering a clearer understanding of the scientific and regulatory

foundations for veterinary medicine approvals within VICH regions. This exchange allows countries outside of VICH to evaluate and incorporate these standards into their own regulatory systems as appropriate, thereby advancing international regulatory alignment and strengthening efforts to safeguard both animal and public health globally (Smith, 2013).

The primary goals of the VICH are to establish harmonized technical requirements for the registration of veterinary medicinal products (i.e. drugs and biologicals, such as vaccines) across VICH member regions, thereby ensuring product quality, safety, efficacy and pharmacovigilance. By standardizing these requirements, VICH aims to reduce unnecessary animal testing and minimize the overall cost and time involved in product development. It serves as a foundation for international regulatory alignment, offering a common basis for product registration across countries. In addition to developing new guidelines, VICH continuously monitors and maintains existing ones, aligning them where appropriate with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) work program. Several of the guidelines developed by VICH, particularly those pertaining to study design, data requirements, and regulatory processes have been adopted or adapted by regulatory authorities in the United States and Europe, facilitating mutual understanding and cooperation in veterinary product evaluation (Bharath *et al.*, 2019).

Guidelines of VICH: VICH has developed a series of Guidelines (GLs) to promote harmonized technical requirements for the registration of veterinary medicinal products across regions. These guidelines span a broad range of subject areas including analytical validation, stability testing, residue safety, pharmacovigilance, efficacy, environmental impact, and electronic data standards. While the majority of the guidelines have been officially adopted and published, certain GLs such as GL25, GL26, GL34, GL41, GL42, GL50, GL55, and GL59 remain either unpublished, not adopted, or are currently pending publication due to

ongoing evaluations or revisions. Among the numerous VICH guidelines, GL9 (Good Clinical Practices), GL24 (Management of Adverse Event Reports), GL29–GL30 (Pharmacovigilance), GL43 (Target Animal Safety), GL46–GL49 (Residue Kinetics and Depletion Studies), and GL51 (Statistical Evaluation of Stability Data) are considered particularly pivotal due to their central role in ensuring the safety, quality, and efficacy of veterinary products (FDA, 2024). Excluding the guidelines that are currently unavailable or pending release, the remaining VICH GLs have been compiled (Supplementary Table 1).

Regional efforts towards harmonization: Regional harmonization of veterinary medicinal product (VMP) regulation plays a crucial role in improving animal health systems, facilitating trade, and enhancing access to quality veterinary medicines (Pyatt *et al.*, 2025). While VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) provides global guidance, many regions adopt and adapt these standards to suit their specific regulatory, agricultural, and economic contexts (WOAH, 2018). In that sense, regional organizations play a vital role in harmonizing veterinary vaccine standards globally (Domenech *et al.*, 2006).

In the European Union, regional integration in veterinary vaccine regulation is well established, with the European Medicines Agency (EMA) coordinating centralised marketing authorisation procedures, the Committee for Medicinal Products for Veterinary Use (CVMP) conducting scientific evaluations, and the European Commission granting marketing authorisations within the framework of EU veterinary medicinal product legislation (EMA, 2019; 2022; 2023). The EMA harmonizes regulatory bodies, ensuring the safety and quality of medicines across the EU, while the European Pharmacopoeia standardizes national laws for medicine manufacture and distribution (Ahmed, 2024). Although these efforts align with VICH, the EU has additional requirements like the Veterinary Medicinal Products Regulation, Union Product Database and strengthened pharmacovigilance networks, creating one of the most harmonized markets globally (EMA, 2022; 2026a). One important effect of harmonized pharmaceutical law in Europe was the introduction of the mutual recognition principle for Official Control Authority Batch Release (OCABR) and Official Batch Protocol Review (OBPR) certificates among EU member states, which facilitates the testing of veterinary immunological products (Pasik and Łysiak, 2019).

In the Americas, organizations like the Pan American Health Organization (PAHO), Inter-American Institute for Cooperation on Agriculture (IICA), and the Committee of the Americas for Veterinary Medical Products (CAMEVET) work to standardize and harmonize the registration and control of veterinary medicines to facilitate regional trade.

While Asia, the Far East, and Oceania currently lack a direct vaccine standardization body, past efforts by the Animal Production and Health Commission for

Asia and the Pacific (APHCA) involved indirect vaccine testing and ongoing initiatives focus on capacity building and information exchange (Tounkara *et al.*, 2021).

In Southeast Asia, ASEAN countries have initiated harmonization efforts informed by VICH principles, though tailored to regional diversity. Through platforms like the ASEAN Regulatory Harmonization Steering Committee for Veterinary Products, member states are working towards common technical requirements and mutual recognition agreements (MRAs) that streamline cross-border registration while preserving national authority (Organization, 2020). Similar MRA systems exist in the West African Economic and Monetary Union (WAEMU, UEMOA) and in the East African Community (EAC).

In Africa, the Pan African Veterinary Vaccine Centre (PANVAC) ensures the availability of safe, effective, and affordable vaccines and reagents by providing independent quality control, standardizing production, and harmonizing quality control techniques through reference materials and training programs, significantly improving vaccine pass rates from African laboratories (Tounkara *et al.*, 2021).

Regions like Africa, Latin America, and the Middle East are developing harmonization strategies, often with support from the African Medicines Regulatory Harmonization (AMRH) initiative, PANDRH, or the Gulf Cooperation Council (GCC). Though not VICH members, these regions are engaging in convergence efforts through regional platforms and capacity-building projects (Calder, 2016; Hettige, 2023).

While regional harmonization efforts vary in scope and maturity, they collectively reflect a growing global movement toward more unified veterinary regulatory framework. Sustained collaboration and alignment with international standards, particularly those established by VICH, are essential for ensuring the safety, quality, and accessibility of veterinary medicines worldwide. Importantly, these regional initiatives do more than strengthen domestic regulatory capacity. They also lay a critical foundation for global convergence through mechanisms like mutual recognition agreements (MRAs) and shared data frameworks (De Brito *et al.*, 2016). By aligning technical requirements and fostering trust among regulatory authorities, these efforts support the development of global data-sharing ecosystems, reducing duplicative evaluations and enabling faster access to high-quality veterinary products across borders (Janse, 2024). Platforms such as VICH, along with international collaborations led by WHO, WOAH, and FAO, serve as key conduits for integrating regional insights into globally accessible regulatory intelligence (Sander, 2025).

One Health initiatives bridging human and animal vaccine regulation: The One Health (OH) approach is an integrated and unifying framework that seeks to optimise the health of people, animals (both domestic and wild), plants, and ecosystems, recognising their interconnectedness and interdependence (Adisasmito *et al.*, 2022). It addresses complex, global challenges such as emerging zoonotic diseases and antimicrobial

resistance (AMR) that cannot be effectively managed within siloed disciplines (Mumford *et al.*, 2023).

Originally introduced as "One Medicine" by Calvin W. Schwabe in 1964 and later advanced through the Manhattan Principles (2004), OH advocates for cross-sectoral and multidisciplinary strategies. Support from global organisations such as WHO, FAO, WOA, and the One Health High-Level Expert Panel (OHHLEP), established in 2021, has further driven coordinated global responses, particularly in zoonotic disease prevention and surveillance (Brown *et al.*, 2024).

The One Health Joint Plan of Action (OH JPA) 2022–2026, developed collaboratively by the Quadripartite organizations (FAO, WHO, WOA, and UNEP) provides an integrated framework to strengthen global efforts in preventing, detecting, and responding to health threats at the human-animal-environment interface. This plan outlines six key action tracks focusing on enhancing One Health capacities, reducing zoonotic disease risks, controlling endemic diseases, ensuring food safety, combating antimicrobial resistance (AMR), and integrating environmental considerations (Milazzo *et al.*, 2025). Central to the OH JPA is regulatory collaboration, where these organizations collectively advocate for and support policy and legislative frameworks that enable coordinated responses to zoonotic disease threats. By offering technical assistance and facilitating knowledge exchange, the plan promotes strengthened health systems and multi-sectoral cooperation. At national and regional levels, countries are encouraged to develop or adapt One Health action plans aligned with the OH JPA's goals, fostering integrated health governance. Regional workshops, such as the Asia-Pacific Quadripartite One Health Workshop, further advance collaboration among human, animal, and environmental health sectors. The joint efforts of WHO, WOA, FAO, and UNEP under the OH JPA exemplify a unified global commitment to holistic health security (FAO, 2022).

Vaccines against diseases transmitted from animals to humans are a critical component of the "One Health" paradigm, which emphasizes collaborative efforts across multiple disciplines to achieve optimal health for people, animals, and the environment (Ahmed *et al.*, 2025). Cross-species vaccination efforts through shared vaccination platforms are highly relevant to the One Health approach. Traditionally, human and animal health industries operate separately, with no organized approach for developing vaccines to prevent the spread of diseases from animals to humans. This segregation can lead to wasted resources and duplicated scientific endeavours. However, integrated efforts, such as the co-development of the West Nile vaccine for both veterinary and human use, demonstrate a more efficient strategy that benefits both commercial opportunities and public health (Roth, 2011). The development of animal vaccines generally has shorter timelines and lower costs compared to human vaccines, which could lead to rapid and inexpensive advances in public health. Furthermore, data from veterinary vaccine development can inform human vaccine programs, providing valuable information on safety, immunity durability, and correlates of protection (Monath, 2013).

Significant progress has been made in vaccine development, yet challenges persist, necessitating collaboration between human and veterinary infectious disease experts to prepare for emerging diseases. Veterinary vaccines must meet high standards for purity, safety, potency, and efficacy, remain affordable for widespread adoption, and be produced under strict manufacturing standards. Regulatory processes need to be efficient while ensuring thorough evaluation, and keeping vaccine costs low will promote broader use, reduce antibiotic reliance, and support food safety vaccines that benefit public health (Roth, 2011).

In recent years, OH is part of a broader shift towards holistic health paradigms such as EcoHealth, Planetary Health, and conservation medicine. EcoHealth explores links between ecological systems and human health (Harrison *et al.*, 2019). Planetary Health focuses on the health of human civilization and the natural systems it relies on, viewing the preservation of these systems as essential for human survival and prosperity, especially amid global environmental changes like climate change (Lebov *et al.*, 2017). Conservation Medicine integrates veterinary medicine, conservation biology, and ecology to study and manage wildlife and ecosystem health, especially concerning biodiversity loss and disease, ultimately aiming to develop solution-oriented approaches for health problems from environmental change (Daszak *et al.*, 2004). These paradigms share the belief that human, animal, and environmental health are interdependent and that integrated approaches foster the value of interdependent, interdisciplinary health governance.

Importance of preparedness for transboundary and emerging animal diseases: Emerging Infectious Diseases (EIDs) and Transboundary Animal Diseases (TADs) represent critical and growing threats to global health, agriculture, economies, and food security (Edo and Bekele, 2019). EIDs refer to diseases that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range. TADs, often overlapping with EIDs, are highly contagious diseases of livestock that can cross borders and spread rapidly, leading to devastating socio-economic and public health impacts. The rise of globalization, climate change, urbanization, and increased movement of people, animals, and goods has heightened the frequency and spread of both EIDs and TADs (Yadav *et al.*, 2020).

Diseases such as avian influenza, African swine fever, and foot-and-mouth disease illustrate how quickly these pathogens can disrupt trade, reduce livestock productivity, and pose zoonotic risks (Brown *et al.*, 2021; McElwain and Thumbi, 2017; Soomro *et al.*, 2023). Historical events such as the Rinderpest pandemic in the 1890s, which led to the death of over 2.5 million cattle in Africa and triggered famines, highlight the devastating consequences of uncontrolled disease spread. It demonstrated the severe toll of unpreparedness, including mass animal deaths, food shortages, and human suffering. Despite successful eradication efforts like the Pan-African Rinderpest Campaign that is estimated to have

brought benefits worth over 35 million European currency units, the challenge remains in prioritizing diseases with low mortality or limited visibility in economically disadvantaged regions. Addressing these challenges requires inclusive approaches such as participatory epidemiology and targeted studies on smallholder impacts (Clemmons *et al.*, 2021).

The unpredictable nature and growing frequency of EIDs and TADs underscore the critical need for robust preparedness strategies. Preparedness involves a multifaceted strategy, including early detection, rapid diagnostics, robust surveillance systems, and international coordination. Strengthening ecological understanding, pathogen evolution monitoring, and disease surveillance systems is essential (Brookes *et al.*, 2015).

Developing countries, in particular, require enhanced veterinary infrastructure, routine mock drills, and fair compensation schemes to encourage timely disease reporting (Yadav *et al.*, 2020). Preparedness also involves transitioning veterinary services towards integrated roles in inspection, surveillance, and quality assurance. Strengthening veterinary infrastructure, investing in effective vaccines, building diagnostic capacity, and enhancing communication between sectors and countries are essential to mitigate risk (Brookes *et al.*, 2015).

A significant barrier to effective TAD control is the lack of reliable, accessible diagnostics and vaccines. Diagnostic tools must be highly accurate, affordable, and distinguish between clinically similar diseases. High mutation rates, particularly among RNA viruses, demand continuous monitoring and innovation in vaccine development to outpace viral evolution (Das *et al.*, 2024). Investment in portable diagnostic tools such as pen-side tests and lab-on-chip technologies is vital to enable flexible and rapid field detection. Improved animal models are essential for understanding disease mechanisms and evaluating intervention strategies. These models should closely replicate natural disease progression to ensure relevance (Clemmons *et al.*, 2021).

Regional cooperation is equally critical. Shared resources such as vaccine banks, disease data dashboards, and cross-border surveillance frameworks can enable a faster and more unified response. Programs aligned with the One Health approach which integrates human, animal, and environmental health offer sustainable solutions to these complex threats (Gongal *et al.*, 2022).

Comprehensive preparedness is not only crucial for national disease management but also for maintaining transparency, fostering international trust, and ensuring coordinated global responses to both EIDs and TADs (Tounkara *et al.*, 2019). Overall, strengthening EIDs and TADs is not only a national responsibility but a global imperative. Strengthening EIDs and TADs preparedness, calls for integrated efforts in diagnostics, vaccine development, animal model refinement, surveillance and coordinated international policy action to reduce both immediate and long-term impacts (Yadav *et al.*, 2020).

Regulatory Challenges in Veterinary Vaccine Approval

Species variability and model limitations: As highlighted in Section 2.2, species variability and species-specific diseases present significant challenges in the development and approval of veterinary vaccines. In contrast to human vaccines, veterinary vaccines must be specifically designed for a wide array of animal species, each possessing distinct immunological responses and disease susceptibilities. It is essential to acknowledge that these vaccines must take into account the unique physiological and immunological features inherent to each species. Such variations play a crucial role in determining the safety, immunogenicity, and overall effectiveness of a vaccine (Francis, 2020).

This interspecies diversity adds complexity to the selection of appropriate animal models for preclinical trials, making it difficult to accurately predict vaccine performance across different target species (Thomas *et al.*, 2022). Furthermore, for many animals, immune correlates of protection remain poorly characterized, necessitating that novel vaccine candidates undergo empirical testing. This lack of standard immune benchmarks also hinders the ability to generalize findings or apply results across species boundaries (Chambers *et al.*, 2016).

Cost and logistics of large-scale animal studies: Among the most critical regulatory barriers are the substantial financial and logistical demands associated with conducting large-scale efficacy trials, which directly impact the ability to meet regulatory requirements for vaccine approval.

Unlike human clinical trials, veterinary vaccine studies require substantially larger animal cohorts and specialized infrastructure, which significantly escalates both costs and logistical complexity. For example, in field trials testing bovine TB vaccines, researchers estimated that demonstrating transmission reduction across herds would require tens of thousands of animals (up to 100,000 cattle across 500 farms), making such large-scale efforts financially prohibitive. Hence, an even smaller, controlled efficacy trials with 200 animals were recommended instead, highlighting the scalability problem (Conlan *et al.*, 2018). In addition to the scale of animal trials, logistical demands such as transportation, housing, feeding, and long-term monitoring require well-equipped facilities and coordinated management, posing significant operational challenges (FAO, 2013).

Moreover, regulatory requirements and batch consistency are crucial and costly. Veterinary vaccines often undergo reassessment to meet shifting guidelines, inflating expenses and project timelines, especially for minor species where market incentives and return on investment are low. Production-grade facilities compliant with Good Manufacturing Practices (GMP) and conventional biosecurity standards introduce additional financial and operational demands (Heldens *et al.*, 2008; Scudamore, 2007). Country-specific trial logistics further complicate matters. A field study in Ethiopia on Peste des Petits Ruminants (PPR) vaccination showed how

costs accumulate, from cold chain storage and transport to mobilization, personnel costs, and farmer opportunity costs (Lyons *et al.*, 2019).

These financial and logistical hurdles not only delay or deter the development of veterinary vaccines, particularly for diseases affecting low-return or marginalized animal populations, but also limit the feasibility of meeting regulatory standards, underscoring the need for supportive frameworks and incentives to enable equitable veterinary vaccine innovation and approval.

Impact of vaccine and logistical/response delays on outbreak control: During outbreaks, the urgency of vaccine deployment often clashes with the prolonged timelines required for regulatory review and approval. When compounded by response delays caused by logistical constraints, the severity of the outbreak can escalate. These challenges are further intensified in regions lacking fast-track approval mechanisms or emergency use provisions, where vaccines may arrive only after the outbreak has peaked or subsided, undermining containment efforts (Klinkenberg *et al.*, 2005). This delay presents a critical challenge in the control of livestock disease outbreaks, particularly in the case of highly transmissible pathogens such as foot-and-mouth disease (FMD). The experience of the 2001 FMD outbreak in the United Kingdom highlighted the devastating economic, logistical, and epidemiological consequences of delayed interventions (Bourn, 2002).

As shown in a modelling study specific to simulated outbreaks of FMD in Scotland, having an initial vaccine stock of 200,000 doses which is enough to vaccinate approximately 12% of the national cattle population, was sufficient to maximize the benefits of vaccination (Porphyre *et al.*, 2018). However, the benefits of vaccination are closely tied to the availability of sufficient initial vaccine stock, the speed of restocking and field implementation. Even a two-week delay in vaccine replenishment, especially when starting with limited doses, can greatly increase epidemic costs. Additionally, delays in deciding when to initiate vaccination and low vaccine efficacy can diminish its overall impact.

Adding to these findings, recent analysis of the 2001 UK outbreak emphasized the often-overlooked impact of logistical delays in culling and carcass disposal (Tao *et al.*, 2021). While depopulation of infected premises is a cornerstone of outbreak response, delays in carrying out these activities, driven by factors such as farm size, remote location, limited resources, and management bottlenecks can dramatically reduce the effectiveness of control strategies. These delays worsened as outbreaks progressed, creating a feedback loop of increased infection and overwhelmed control efforts.

Together, these two bodies of evidence stress the importance of integrating both vaccine availability and logistical capacity into outbreak preparedness plans. While vaccine delays influence the choice and success of vaccination-based interventions, delayed culling and disposal actions affect the trajectory of any control strategy, regardless of the method used. Effective outbreak modelling and response planning must move beyond idealized assumptions and incorporate

dynamic, context-specific constraints (Tao *et al.*, 2021). Inferring from the previous cited references and studies on Ebola and COVID-19 outbreaks, tailored strategies such as prioritizing large farms, investing in rapid-response infrastructure, and allocating sufficient pre-outbreak resources, can help mitigate the compounding risks posed by operational delays (Baral, 2021; Kass *et al.*, 2019).

Regulatory disparities and the need for harmonized emergency pathways: Differences in national and regional regulatory frameworks continue to present major challenges in the development, approval, and timely deployment of veterinary vaccines. Although many countries base their assessments on internationally accepted scientific principles, the regulatory requirements for safety, efficacy, and manufacturing practices still vary considerably between jurisdictions. This lack of harmonization often compels manufacturers to repeat preclinical and clinical evaluations for each target market, thereby increasing the time, cost, and complexity of bringing a vaccine to global markets (Bielitzki *et al.*, 2007).

A particularly pressing concern emerging from these disparities is the absence of harmonized emergency use authorization (EUA) pathways in many countries. While some regions, such as the European Union and America, have established structured frameworks for conditional or emergency vaccine approvals, many countries, particularly in low- and middle-income settings, lack clearly defined, harmonized pathways to authorize vaccines rapidly during crisis situations (Tounkara *et al.*, 2021). The absence of science-based, fast-track mechanisms and awareness hinders swift responses to emerging infectious diseases (EIDs) and transboundary animal diseases (TADs), delaying the deployment of critical interventions when time is of the essence (Yadav *et al.*, 2020).

This knowledge gap in understanding impacts collaboration and becomes especially problematic in regions with limited regulatory infrastructure, where emergency use authorizations are either underdeveloped or inconsistently applied (McPake *et al.*, 2022). In the absence of harmonized standards, national authorities may selectively adopt regulations best suited to their local context, which can lead to reluctance in accepting foreign data or fast-tracking approvals for vaccines validated elsewhere. This regulatory fragmentation often results in duplicated efforts, inconsistencies in vaccine quality control, and delays that hinder timely disease containment (Metwally *et al.*, 2021).

Although international organizations like the VICH and WOAHP provide foundational technical guidelines, their adoption remains uneven. Regional efforts such as ASEAN, CAMEVET, and AU-PANVAC offer encouraging examples of collaboration and standard-setting, but disparities in capacity, legal frameworks, and political commitment still pose obstacles (Ncube *et al.*, 2021). For example, while Africa's PANVAC supports standardization and quality control for veterinary vaccines, a harmonized emergency authorization protocol across African nations is still lacking (Jaime *et al.*, 2022).

This fragmentation is particularly concerning in the face of zoonotic threats and rapidly evolving pathogens, where global preparedness relies on timely, coordinated action. As highlighted in Section 5.5, the unpredictable nature of EIDs and TADs underscores the urgent need for proactive emergency regulatory mechanisms. Delays caused by absent or misaligned frameworks not only affect animal health but also compromise One Health objectives, public health security, and food systems resilience. Developing universal principles for emergency authorization and vaccine development pipeline supported by mutual recognition agreements and real-time data sharing platforms, is essential to streamline approvals and accelerate access to veterinary vaccines during high-risk outbreaks (Bielitzki *et al.*, 2007).

Conclusion and Future Perspectives

Veterinary vaccines play a critical role in controlling epizootic and zoonotic diseases, ensuring food security, and protecting public health. Despite their importance, regulatory frameworks for veterinary vaccine registration vary significantly across regions, leading to delays and challenges in global access and harmonization. A streamlined, science-based, and species-specific approach to regulation is essential to overcome these disparities. Looking ahead, there is a pressing need to invest in veterinary-specific regulatory science and infrastructure to meet the unique challenges of animal vaccine development. The adoption of digital submissions and AI-assisted regulatory reviews can enhance the efficiency and transparency of approval processes. Fast-track approval systems tailored for outbreak scenarios, particularly for transboundary diseases are crucial for rapid response in endemic and high-risk regions. Public-private partnerships should be fostered to drive innovation in veterinary vaccine technologies, including DIVA and marker vaccines. Furthermore, global collaboration through harmonized frameworks, mutual recognition agreements, and One Health initiatives must be strengthened to facilitate vaccine access across borders. Ultimately, building a robust yet adaptable regulatory ecosystem will ensure the timely availability of safe and effective veterinary vaccines while preserving scientific integrity and public trust.

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Supplementary Table S1 VICH guidelines.

VICH GL No.	CVM GFI No.	Focus Area	Significance
GL1 / GL2	#63 / #64	Validation of Analytical Procedures: Definitions and Methodology	Ensures reliable, reproducible analytical methods for quality control
GL3(R)	#73	Stability Testing of New Veterinary Drug Substances and Medicinal Products	Establishes protocols to determine product shelf life and formulation integrity
GL4	#74	Stability Testing of New Veterinary Dosage Forms	Evaluates stability of veterinary drug products in their final dosage forms
GL5	#75	Stability Testing – Photostability Testing of New Veterinary Drug Substances and Medicinal Products	Provides protocols for assessing light sensitivity of drug substances and products
GL6	#89	Environmental Impact Assessments (EIA) – Phase I	Describes initial screening steps to evaluate environmental risk
GL7	#90	Effectiveness of Anthelmintics – General Recommendations	Establishes baseline standards for evaluating antiparasitic efficacy
GL8	#91	Stability Testing for Medicated Premixes	Outlines stability testing requirements for medicated feed premixes
GL9	#85	Good Clinical Practices	Defines standards for ethical and scientific conduct of veterinary clinical trials
GL10(R)	#92	Impurities in New Veterinary Drug Substances	Sets thresholds and reporting standards for impurities in APIs
GL11(R)	#93	Impurities in New Veterinary Medicinal Products	Extends impurity guidance to finished veterinary medicinal products
GL12	#95	Anthelmintic Efficacy: Specific Recommendations for Bovines	Provides species-specific guidelines for testing antiparasitic efficacy in cattle
GL13	#96	Anthelmintic Efficacy: Specific Recommendations for Ovines	Specifies efficacy standards for antiparasitic in sheep
GL14	#97	Anthelmintic Efficacy: Specific Recommendations for Caprines	Addresses testing requirements for goats
GL15	#109	Anthelmintic Efficacy: Specific Recommendations for Equines	Details antiparasitic efficacy protocols for horses
GL16	#110	Anthelmintic Efficacy: Specific Recommendations for Porcines	Provides guidance for pigs
GL17	#99	Testing of New Biotechnological/Biological Veterinary Medicinal Products	Describes evaluation requirements for new biotech-based veterinary products
GL18(R2)	#100	Impurities – Residual Solvents in Veterinary Medicinal Products, Active Substances and Excipients	Harmonizes solvent residual limits in line with human ICH guidance
GL19	#111	Anthelmintic Efficacy: Specific Recommendations for Canines	Defines protocols for antiparasitic testing in dogs
GL20	#113	Anthelmintic Efficacy: Specific Recommendations for Felines	Establishes testing standards for cats
GL21	#114	Anthelmintic Efficacy: Specific Recommendations for Chickens (<i>Gallus gallus</i>)	Tailors efficacy testing for poultry
GL22 (R1)	#115	Reproduction Toxicity Testing – Safety of Residues in Human Food	Part of food safety assessment for drug residues
GL23 (R2)	#116	Genotoxicity Testing – Safety of Residues in Human Food	Evaluates potential DNA damage from residues
GL24	#117	Management of Adverse Event Reports (AERs)	Details collection, assessment, and submission of adverse event data
GL27	#144	Pre-Approval Information for Antimicrobial Resistance	Addresses data requirements for antimicrobial resistance risk assessment in food-producing animals
GL28	#141	Carcinogenicity Testing – Safety of Residues in Human Food	Provides testing requirements to assess cancer risk from drug residues in food-producing animals
GL29	#142	Pharmacovigilance: Periodic Summary Update Reports (PSURs)	Defines format and content for periodic safety reporting post-approval
GL30	#143	Pharmacovigilance: Controlled List of Terms	Offers standardized vocabulary for adverse event and safety reporting
GL31	#147	Repeat-Dose (90-Day) Toxicity Testing – Residue Safety	Establishes chronic toxicity testing protocols for evaluating residue safety
GL32	#148	Developmental Toxicity Testing	Details requirements for assessing risk to offspring during drug exposure
GL33	#149	General Approach to Residue Safety Testing	Integrates multiple toxicity studies to assess overall residue safety
GL35	#214	Electronic Standards for Transfer of Data	Promotes standardized electronic submission formats
GL36	#159	Microbiological ADI – General Approach	Describes methodology to establish microbiological Acceptable Daily Intakes (ADIs)

VICH GL No.	CVM GFI No.	Focus Area	Significance
GL37	#160	Chronic Toxicity Testing – Residue Safety	Provides framework for repeat-dose long-term toxicity testing
GL38	#166	Environmental Impact Assessment (Phase II)	Details advanced studies to assess potential environmental risks of veterinary medicinal products
GL39	#176	Specifications: Test Procedures and Acceptance Criteria – Chemical Substances	Defines how quality specifications are developed and validated
GL40	#177	Specifications: Biotechnological/Biological Veterinary Products	Tailors quality criteria for biological/biotech-based veterinary products
GL43	#185	Target Animal Safety for Veterinary Pharmaceutical Products	Outlines required safety data for intended animal species
GL44	#196	Pharmacovigilance: Data Elements for Adverse Event Reporting	Provides structured formats for consistent global post-market safety surveillance
GL45	#198	Bracketing and Matrixing Designs for Stability Testing	Offers advanced strategies for efficient stability testing design
GL46	#205	Metabolism Study to Determine Quantity and Nature of Residues	Supports food safety assessments by characterizing residue composition in edible tissues
GL47	#206	Comparative Metabolism Studies in Laboratory Animals	Assesses relevance of animal residue studies to human health
GL48	#207	Marker Residue Depletion Studies – Establishing Withdrawal Periods	Helps set withdrawal periods to ensure drug residues are below safe limits before animal products enter food
GL49	#208	Validation of Analytical Methods in Residue Depletion Studies	Ensures analytical methods used in food safety studies are validated and reliable
GL51	#219	Statistical Evaluation of Stability Data	Guides data analysis to ensure reliable stability testing conclusions
GL52	#224	Bioequivalence: Blood Level Bioequivalence Studies	Guides demonstration of equivalence for generics through blood level pharmacokinetic studies
GL53	#225	Electronic Exchange of Documents: File Format Recommendations	Recommends standardized file formats for electronic document submissions, improving regulatory consistency
GL54	#232	Establishing an Acute Reference Dose (ARfD) – Residue Safety	Describes approach to determine ARfD values for veterinary drug residues in human food
GL56	#243	Residue Studies in Honey – Design Recommendations	Provides study design guidance to determine withdrawal periods and MRLs for honey
GL57	#257	Residue Depletion in Aquatic Species – Marker Residue Studies	Outlines protocols for establishing withdrawal periods in fish and other aquatic food-producing animals
GL58	#259	Stability Testing in Climatic Zones III and IV	Specifies stability-testing requirements under hot and humid climatic conditions, crucial for tropical regions
GL60	#286	Good Manufacturing Practices for Active Pharmaceutical Ingredients	Introduces harmonized GMP standards to ensure quality of veterinary APIs
GL61	#290	Pharmaceutical Development	Provides a structured approach for developing veterinary medicinal products, aligning with ICH Q8 concepts

*ADI, Acceptable Daily Intake; AER, Adverse Event Report; API, active pharmaceutical ingredient; ARfD, Acute Reference Dose; CVM, Center for Veterinary Medicine; DNA, deoxyribonucleic acid; EIA, Environmental Impact Assessment; GFI, Guidance for Industry; GL, Guideline; GMP, Good Manufacturing Practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MRL, Maximum Residue Limit; PSUR, Periodic Safety Update Report; VICH, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.