Review of updated regulations and product license categories for veterinary vaccines in the United States

Matthew M. Erdman DVM, PhD
Nancy E. Clough DVM, PhD
Paul J. Hauer DVM, PhD

From the Center for Veterinary Biologics, Veterinary Services, Animal and Plant Health Inspection Service, USDA, Ames, IA 50010 (Erdman, Clough,* Hauer).

Address correspondence to Dr. Erdman (matthew.m.erdman@usda.gov).

*Retired.

In the United States, the regulation of veterinary biologics (vaccines, bacterins, antiserum, diagnostic kits, and other products of biological origin acting through immunologic mechanisms for the prevention, treatment, or diagnosis of animal disease) is mandated under the VSTA, and the VSTA prohibits the preparation or sale of veterinary biologics that are worthless, contaminated, dangerous, or harmful. These requirements are typically interpreted to mean that products should be pure, safe, potent, and efficacious. The VSTA is implemented by the USDA on the basis of requirements described in 9 CFR 101–124, and the USDA APHIS CVB provides regulatory oversight for veterinary biologics. Overall, when this report was written, there were 89 manufacturers with 1,583 active licensed veterinary biologics with product claims for 357 unique organisms or diseases in 31 unique targeted animal species. Many products have claims for > 1 organism or disease, some organisms might cause > 1 disease, and some products include claims for > 1 targeted animal species.

In contrast to veterinary biologics, for which USDA APHIS CVB provides regulatory oversight, veterinary drugs are regulated by the FDA under the Federal Food, Drug and Cosmetic Act, and the Animal Drug Availability Act. As biotechnology and innovation advance, new products sometimes require a jurisdiction determination between the USDA and FDA, the basis of which is beyond the scope of this article.

The goal of any regulatory program should be to balance the legal requirements of oversight with the needs of the stakeholders. In the case of veterinary biologics, some aspects of product licensure may need to be flexible to meet special or urgent needs of veterinarians, clients, or patients. Although diminished safety or purity would rarely, if ever, be considered, flexibility may be applied to aspects of licensure, such as demonstration of efficacy or potency testing. The USDA uses licensing categories with various levels of data requirements to issue a product license. This flexibility is allowed under 21 USC §154a, which describes special licenses for special circumstances or conditions. In 1985, options for licensure of conditional and autogenous products were added to the existing regulations of traditional full licensure. More recently, the USDA created new subcategories for platform and prescription platform products on the basis of established VESs, standardized manufacturing systems, and other specific requirements described later. The purpose of this report was to provide updates on the recent CVB program changes pertaining to the regulatory categories of veterinary biologics, focusing on US veterinary vaccine license categories (Table 1).

Vaccine License Categories

Regulatory oversight of veterinary vaccines focuses on multiple components. Manufacturing facilities are inspected before a manufacturer is issued its first product license and on a periodic, unannounced basis thereafter, to ensure that personnel are trained and that the facility is adequately equipped and maintained. Starting materials (eg, seed bacteria or viruses and cell lines) for manufacturing are tested by the manufacturer and then retested by the CVB to ensure identity and purity. Seed bacteria used to make non-inactivated vaccines are evaluated for the presence of antimicrobial-resistance genes. Seeds made with recombinant DNA techniques are evaluated on a molecular basis for protein expression and genetic stability. Live, vectored vaccines require environmental...
assessments to comply with the NEPA and also may require safety studies in nontarget species (species that may come into contact with vaccinated animals) and studies to demonstrate that the seed does not revert back to a virulent state once in an animal.

Consistency in the manufacturing process is a key component to the regulatory process; no substantial changes in manufacturing are allowed from the formulation used in licensing studies, and manufacturing methods must be documented in a production outline. Multiple batches of product, already tested by the manufacturer, are retested by the CVB prior to licensing, and samples from every batch of most products are submitted to the CVB for possible random testing after licensure. Additionally, samples of each batch of product are retained through the product's expiration date so that follow-up testing may be performed should a problem occur.

**Fully licensed products**

Fully licensed products remain the cornerstone of veterinary vaccines in the United States. Of the 1,134 vaccines licensed for use in animals in the United States, 1,107 were fully licensed when this report was written. Products with full licenses, compared with a license in another category, undergo the most rigorous analyses in terms of efficacy and safety. Nearly all fully licensed vaccines undergo a successful, statistically valid vaccine-challenge study in an appropriate host animal challenge model that uses animals of the minimum age recommended on the given product label. In instances for which such challenge models do not exist, a much larger field efficacy study may be used to evaluate the product through natural exposure to the disease. Once efficacy has been demonstrated, products are evaluated for safety under field conditions. Safety studies generally require ≥ 600 animals of the target species with a third or more of the animals at the minimum age for which the product will be recommended, and such studies must be conducted in 3 different geographic locations. For all licensing studies, study reports (including raw data and analyses) are reviewed by the CVB for scientific soundness of study design and for clinical relevance and statistical precision of findings.

**Conditionally licensed products**

The intent of conditional licenses, as described in 9 CFR 102.6, is "to meet an emergency condition, limited market, local situation, or other special circumstance." Conditionally licensed vaccines generally do not yet meet the efficacy requirements for full license but demonstrate a "reasonable expectation of efficacy" and fully meet safety requirements. Acceptable methods for demonstrating a reasonable expectation of efficacy vary on a case-by-case basis and may include use of host animal challenge or field studies in a limited number of animals, evaluation of serologic data when serology is adequately correlated to efficacy, or other methods that indicate a beneficial result from vaccination with the product.

Nonrecombinant vaccines against infectious disease agents typically qualify for a conditional license if there are no equivalent fully licensed products approved for a particular indication in the United States. Conditional licenses are typically sought as a first step for mitigating spread or impact of newly emerging animal diseases, as was the case for porcine epidemic diarrhea virus, canine influenza virus, and West Nile virus. In addition, products for niche markets where potential sales may not support the investments required for full efficacy studies may be allowed conditional licenses in some instances. After a conditional license is granted, the manufacturer is expected to work toward achieving a full license for the product, and unlike full licenses, conditional licenses expire and must be renewed every 1 to 2 years. In addition, once a fully licensed product becomes available for a particular indication, conditionally licensed products for that same indication must also progress to fully licensed products or their conditional licenses will not be renewed.

**Autogenous products**

Autogenous vaccines are products prepared from organisms that were obtained from the animals, herd, or flock to be vaccinated. The widespread use of custom or autogenous vaccines started with the practice of feeding pregnant sows virulent cultures of *Escherichia coli* that had been isolated from neonatal pigs with diarrhea, thereby enhancing colostral concentrations of maternal antibodies in treated sows and

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**Table 1—Comparative overview of the CVB regulatory requirements pertaining to safety, efficacy, and potency studies and distribution restrictions for veterinary biologics grouped by license category.**

<table>
<thead>
<tr>
<th>License category</th>
<th>Target animal safety study</th>
<th>Efficacy study</th>
<th>Validated potency testing</th>
<th>Restricted distribution or use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Conditional</td>
<td>Yes‡</td>
<td>Yes§</td>
<td>No</td>
<td>Yes†</td>
</tr>
<tr>
<td>Autogenous</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Platform</td>
<td>Yes§</td>
<td>Yes‡</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prescription platform</td>
<td>Yes§§</td>
<td>Yes‡‡</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Partial evaluation is required. †Use requires permission from the given state veterinarian. ‡Full study is required for the original platform product. §One safety study per target species with use of maximum antigen concentration per dose.
boosting transfer of immunity to their piglets. Anecdotally, reports of efficacy from matched, herd-of-origin cultures were recognized prior to the development of the typing scheme of fimbriae and other immunogens important in strain-specific E coli immunity. Such vaccines were excluded from licensing requirements, and over time, veterinary practices also prepared herd-specific vaccines for other diseases. In 1987, the USDA codified in 9 CFR 107.1 specific exceptions for regulatory oversight of vaccines manufactured by veterinary clinics for use in client-owned animals. In 1992, 9 CFR 113.113 was added to the regulations to require licenses for all autogenous vaccines that were not part of the previously published exemptions and to require all licensed autogenous vaccines to be inactivated products. Guidelines accompanying the regulation are detailed in Veterinary Services Memorandum 800.69. Restrictions for veterinary practice exemptions were adjusted in 2015 so that only products made in the same building as the veterinary practice and that are neither consigned nor subcontracted are exempted from licensing.

Autogenous vaccines are targeted to applications in which either there is no licensed alternative vaccine available or there is a perceived lack of efficacy of licensed products owing to strain differences. Licensed autogenous vaccine manufacturers must justify meat withdrawal intervals on the basis of histologic examinations of injection sites, ensure complete inactivation of the microorganisms used, and test to ensure product batches do not have bacterial or fungal contamination. Autogenous vaccines are tested in mice, poultry, fish, or guinea pigs for safety; however, there are no requirements to demonstrate efficacy or host animal safety for licensed autogenous vaccines. Use of autogenous vaccines is limited to herds or flocks from which the microbial isolates for the vaccine were obtained; adjacent or epidemiologically linked herds or flocks may be vaccinated if approved by the given state veterinarian. There are also time limitations for how long microbial isolates can be used to prepare autogenous vaccines without additional testing to ensure isolates are still relevant to the clinical disease situation.

**Platform products**

The application of biotechnological approaches to veterinary vaccine development continues to advance. A VES is often used to express a recombinant antigen either in vitro or in vivo, and repeated use of a single VES to express different antigens provides an opportunity for standardized manufacturing processes. The USDA refers to vaccines derived from well-characterized VESs and standardized manufacturing methods as platform products and recently began offering an expedited licensing pathway, described in Veterinary Services Memorandum 800.213, for products derived from a licensed platform. Currently, platform products are limited to inactivated or non-replicating products.

By USDA definition relative to vaccines, a platform is comprised of multiple components, including the VES, expressed GMOI for insertion, manufacturing process, and efficacy and safety data associated with fully licensing an initial product. Once these components are established for licensure of an initial product, some licensure requirements (eg, another field safety trial) may be waived for subsequent products that vary only in the expressed GMOI. For example, the CVB has licensed multiple vaccines that use a baculovirus expression system, providing a wealth of data to support the safety and effectiveness of the system to express recombinant antigens. In a simple scenario, a manufacturer might achieve an initial full license for an inactivated vaccine product on the basis of a recombinant baculovirus expressing GMOI that codes for the HA protein of influenza virus. Doing so would establish the platform for that specific manufacturer, who could then with minimal additional regulatory requirements pursue licenses for subsequent vaccines that use the same platform but GMOI for other HA types of avian influenza virus. This manufacturer’s subsequent products may be fully or conditionally licensed, as described earlier. The regulatory path of platform products was designed to facilitate a rapid response to evolving pathogens in the field combined with limited risk of the loss of vaccine safety or efficacy.

**Prescription platform products**

Prescription platform products are extensions of platform products. As described in Veterinary Services Memorandum 800.214, a manufacturer of prescription platform products must first have a licensed platform product on which subsequent products are based. The only aspect of a prescription platform product that can differ from the original on which it is based is the expressed GMOI, and the GMOI is not limited to a variation of the original GMOI. For instance, when we consider the earlier poultry vaccine example, a prescription platform product could use the GMOI that codes for the VP2 capsid protein of infectious bursal disease virus to replace the GMOI that codes for the HA gene of avian influenza virus, whereas a platform product could only swap various GMOIs that code for various HA genes.

Each batch of a prescription platform product is prepared on a custom basis for an individual animal or group of animals after a written prescription order is issued within a valid VCPR by a licensed veterinarian. The animal's needs are the basis for the GMOI to be used in the particular batch of vaccine. The prescribing veterinarian may provide a microbial isolate from which a gene insert will be derived or may work with the manufacturer to select the most appropriate insert from a bank of known gene sequences.

The regulatory focus for prescription platform products is safety, and manufacturers test each batch
for safety and purity. Prior to regulatory approval of a prescription platform product, a host animal safety test that uses a product batch with the highest allowable antigen concentration must be conducted in each species for which the product is intended. Thus, there is an expectation of safety for each prescription platform product. No efficacy claims are allowed for these products because efficacy studies are not conducted; however, there is a precedent that efficacious product was prepared with the sameVES and manufacturing process used to create the original platform product, whereas no such standardization is required for autogenous vaccines. Another difference between prescription platform products and autogenous vaccines is that use of autogenous vaccines is limited to herds or flocks in which the seed organism was obtained or in geographically adjacent herds or flocks, whereas prescription platform products may be used in any animals encompassed in valid VCPRs of the prescribing veterinarian. The regulatory path for prescription platform products provides livestock and poultry producers with flexibility to use vaccine products beyond those commercially available. Because prescribing veterinarians should look for evidence of efficacy to support their decision to continue use of prescription platform products, these products are typically suited for production animal situations in which higher numbers of vaccinates facilitate product performance evaluation, compared with companion animal situations with fewer vaccinates.

**Imported, unlicensed biologics**

In rare situations, unlicensed biologics from foreign manufacturers are approved for importation and use in the United States. This approach is typically considered only when there is a lack of USDA-licensed products, including autogenous products, for an emerging animal disease threat in the United States. Substantial justification is required to use unlicensed imported biologics in animals outside of a formal biological containment facility (eg, biosafety level 1 through 4 research facilities or well-managed livestock containment facilities). Exceptions require detailed documentation describing the intended use, a scientifically defensible statement regarding the lack of available products in the United States, and authorization from the state veterinarian for use of the imported, unlicensed product. Importers may be required to have clients sign informed consent forms stating that the product has not been evaluated or licensed by the USDA, and there may be additional restrictions as deemed necessary by the CVB. In addition, detailed information about the nature and manufacturing process of an imported, unlicensed product is required for a risk assessment because even with the appropriate clinical justification for use, regulatory approval hinges on risks of introducing foreign animal diseases into the United States. Relevant information includes disease status of the country of origin, other organisms present in the manufacturing facility, viability of the product, inactivation procedures, tests to confirm complete inactivation, and the source and testing of any ingredients of animal origin. Because of enhanced risk, the USDA has not historically approved importation of unlicensed products containing live, genetically modified organisms or products that are intended to be administered to animals and that originated from countries with certain foreign animal diseases (eg, foot-and-mouth disease).

When importation is approved, the CVB issues a Permit for Research and Evaluation for the unlicensed product. A Permit for Research and Evaluation is distinct from a Permit for Sale and Distribution, which is issued for importation of a product that meets license requirements for use in the United States. Products imported under a Permit for Research and Evaluation are prohibited from further distribution beyond the permit holder, unless explicitly approved by the CVB. The permit may include additional restrictions, such as requiring a valid VCPR for use of the product or restricting use of the product to identified quarantine zones.

**Updates on Other Recent USDA Initiatives**

**Vaccine labeling**

Regulatory control of labeling of veterinary biologics is in accordance with 9 CFR 112. In 2016, the USDA codified numerous changes for labeling and packaging of veterinary biologic, with full implementation of the changes expected by 2021. One purpose of the labeling and packaging changes was to standardize the format in which licensees present required elements of a veterinary vaccine label. In particular, products that are in full compliance with USDA regulatory requirements can be identified by the presence of the USDA veterinary biologics establishment license number (or USDA veterinary biological product permit number) and product code number (Figure 1). Products that do not have these numbers on the label are not licensed by the USDA and likely do not comply with the USDA’s regulatory requirements.

All licensed vaccines will have labeling with a true name that describes the components of the vaccine. Fully licensed vaccines (except autogenous products) may also have proprietary trade names. In contrast, conditionally licensed products cannot bear trade names, and their labeling must contain a statement alerting the user that the product is conditionally licensed.

Regulations pertaining to single label claim for veterinary biologics were published in 2015. Also known as the single-tier rule, the regulations further standardize product claims for domestically distributed vaccines and immunomodulators. The rule does not apply to autogenous vaccines, serum antibody
Under this rule, the USDA transitions from a previous 4-tier approach to efficacy to the current single-tier approach to efficacy with a statement that includes target species, age of target species to be vaccinated, and the pathogen or disease against which the vaccine is intended (Table 2). The previous 4-tier approach was based on the magnitude of effects (eg, reduce severity vs prevent disease) seen in efficacy studies and often led to confusion or misinterpretation by end users. Instead of trying to differentiate among 4 levels of efficacy claims in a few words on labeling material as was done previously under the 4-tier format, the single-tier rule specifies a single, uniform claim format to be used for all USDA-licensed products subject to the rule. End users are then instructed to read a standardized product study summary for detailed results of the efficacy and safety studies that supported product licensure.

### Product study summaries

The CVB is currently in the process of publishing product study summaries\(^{10}\) as part of the USDA website; a complete collection is expected by the end of 2021. Users may search for any eligible, licensed product on the basis of manufacturer, distributor, microbial agent, trade name, or product number; however, only studies conducted since 2007 will be described in detail. The summaries provide transparency to the data accepted to support licensure. To be as objective as possible, the study summaries provide raw data and sometimes rudimentary data compilation (eg, counts or sums), without elaborate statistical analysis or discussion. The CVB strongly cautions readers against comparing products on the basis of these published study summaries alone. Slight differences in study design, which may not be evident in the study summary, often preclude such comparisons. Also, policies and licensing standards have changed over time; thus, studies may vary on the basis of requirements in place when licensure was obtained.

### NEPA and categorical exclusion

Live recombinant vaccines require evaluation for compliance with the NEPA.\(^{11}\) Historically, a separate environmental assessment, Federal Register publica-
Table 2—Comparison of label claim wording for the current single-tier label format versus the previous 4-tier label format for CVB-licensed vaccines.

<table>
<thead>
<tr>
<th>Label claim format</th>
<th>Vaccines included</th>
<th>Example wording</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single tier</td>
<td>All vaccines</td>
<td>This product has been shown to be effective for the vaccination of healthy dogs 6 wk of age or older against canine distemper virus. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov.</td>
</tr>
<tr>
<td>4 tier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier 1</td>
<td>Vaccines shown to reduce the severity of, but not prevent, disease</td>
<td>For vaccination of healthy dogs as an aid in the control of disease caused by canine distemper virus.</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Vaccines shown to prevent disease, as defined in a study's case definition, in a statistically significant and clinically relevant manner</td>
<td>For vaccination of healthy dogs as an aid in the prevention of disease caused by canine distemper virus.</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Vaccines that meet criteria for tier 2 and for which efficacy studies showed a particularly high level of clinical relevance and statistical significance</td>
<td>For vaccination of healthy dogs for the prevention of disease caused by canine distemper virus.</td>
</tr>
<tr>
<td>Tier 4*</td>
<td>Vaccines demonstrated to prevent animals from becoming infected when exposed to the disease organism</td>
<td>For vaccination of healthy dogs for the prevention of infection with canine distemper virus.</td>
</tr>
</tbody>
</table>

Footnotes


References

1. VSTA, 21 USC §151-159 (2020).
13. USDA APHIS. VSTA records and reports specific to international standards for pharmacovigilance. Fed Regist 2018;83:22882.