Vaccines: What REALLY is in, and on, those bottles?

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Vaccines and vaccination are receiving renewed attention within the veterinary profession. Objective, critical thinking and scrutiny suggest that such a review is long overdue. Some of the concerns surfacing as the scrutiny intensifies include:

- Vaccine associated illnesses, uncertain efficacy data, inaccurate label claims
- Questions on duration of immunity (DOI) claims and actual, medically correct revaccination intervals
- The regulatory process of vaccine approval, the promotion, production and marketing of vaccines are murky and difficult to clearly pin down
- Very thorough and documented guidelines for feline vaccination have been published by the AAFP
- The COBTA of AVMA is concluding a three-year-long study into canine and feline immunization, vaccines and eventual recommendations.
- Four Expert Panels have been convened, communicated and reports are under consideration by the COBTA/DAC
- The ACVIM has reviewed work in the cat, affirmed AAFP's opinion and is on record in support of those recommendations.
- Other species groups, most notably AAEP, are beginning to take note that all is not well in the world of animal vaccines and to critically review many aspects.
- Even with zero efficacy data, the manufacture, promotion and sale of "autogenous" products is burgeoning.
- "Harmonization", the process of trying to make EU and US animal vaccine requirements equivalent and thus allow effective international standards, is underway
- The Federal Preemption is in place, preventing tort claims against vaccine manufacturers by damaged parties
- Lack of an Adverse Event reporting system at the USDA level and no publicly available, transparent data on adverse outcomes associated with vaccination

These notes have as their goal a broad overview and a framework for consideration of the many contemporary issues surrounding vaccines and immunization. The devil, however, is in the details. Even as the critical review of pharmaceuticals and the production of safe food from medically well-cared-for animals emerged as a topic nearly 20 years, so too will the present vaccine concerns demand study and understanding by the profession. There is much to know. Hopefully, this paper can serve as a starting point.

Animal Vaccines in the United States

An important area of veterinary confusion must be noted at the start. Vaccines for humans and pharmaceutical products for both humans and animals are regulated by the Food and Drug Administration. This is not the case with animal vaccines. Animal vaccine regulation and approval is a function of USDA. The US Department of Agriculture, Animal and Plant Health Inspection Service, Center for Veterinary Biologics is a very small agency with the sole responsibility for animal vaccine licensure and approval. The CVB is now headquartered in Ames, IA, having recently moved from Maryland. This agency has a small budget and a small staff, approximately $10 million annually. With this staff and funds, the CVB must exercise regulatory oversight for 110 biologics companies and nearly 2,500 animal vaccine products.

The Council on Biologic and Therapeutic Agents (COBTA/DAC) of the AVMA has begun a most comprehensive and organized review of veterinary vaccines. The endpoint goal of this several year long, continuing effort is **"best patient care"**. In addition, it is the charge of this Council that standardized, general recommendations on vaccine use be written and adopted by AVMA. Much of my information comes from six years of service on that body. These notes are my personal views, based on the learning process in practice and COBTA activity.

In the efforts of COBTA to sort through the issues of vaccine safety and efficacy, many marvelously intertwined and exceedingly complex issues surrounding veterinary vaccines were uncovered. To even begin to

do justice to the topic in this short paper would be impossible. For that reason, critical highlight points are presented. These are items that will provide groundwork for future discussion.

1. Veterinary vaccines are regulated under the 1913 Virus, Serum, and Toxin (VST) Act. While amendments have been added through the years, the VST remains essentially a document of a time past, certainly preceding modern technologic advances. In my opinion, the VST Act serves well as a guideline for commerce in animal vaccines but is woefully inadequate in assuring safety and efficacy for animals or the public.
2. The heart of the 1913 VST Act is the establishment of four criteria for approval. All of the rest of the regulations codified in 9CFR, and other regulations and memos, orbits around these four guiding principles in the act. It is critically important that the profession be aware of these four principles and understand how they relate to the types of vaccine licensure and the details surrounding approval.
   - Purity
   - Potency
   - Safety
   - Efficacy

   These points of importance to licensing and labeling will come up repeatedly in these notes and will be identified via the acronym **"PPSE"**.
3. The difference in regulatory agencies, their missions, their methods, and even their relationship to the profession is vastly different. Some of the confusion may well arise because the Food and Drug Administration, in fact, **does** regulate, approve, and control all human vaccines. While FDA-CVM has a good deal of oversight of the practicing professional, the USDA-CVB primarily interacts with the biologics industry and does not directly regulate distribution or use of biologics. There is no such thing as "Extra-Label Use" with veterinary biologics.
4. There are some striking differences in the management of veterinary vaccines, especially when contrasted to the much more familiar management of veterinary pharmaceuticals.
   a. Unlike pharmaceuticals, there is no mandated adverse reaction or adverse event reporting required for veterinary vaccines. The CVB has no mechanism in place to manage reports from the field aside from accepting them as points of information. The various vaccine companies are encouraged to maintain a file on reported events. That report is to be made available to CVB during routine inspections. The burden of adverse event management thus falls entirely on the regulated industry, the vaccine companies. Each is free to tailor management of such situations as it sees fit, leading to a good deal of confusion in the veterinary profession as to how to best manage an adverse situation.
   b. An obvious outcome is that no publicly available third party disclosure can inform the public or the profession when the response to vaccine goes bad. The historic record is replete with examples of such situations: noncytopathic BVD virus in bovine vaccines; vaccine site reactions associated with use of many products and many species that ended up being a significant and sometimes prolonged issue at slaughter; shock-like reactions associated with *Moraxella bovis*, to name just a few.
5. A key component of vaccine evaluation is efficacy. Unlike pharmaceuticals, any field evaluation of efficacy by the end user is often extremely difficult, if not impossible. The impression may be gained that a vaccine is effective when, in fact, absence of the pathogen, natural or innate immunity, or even the masking of pathogenic effects by other disease provides an appearance of efficacy. In depth discussions with the expert panel of veterinary immunologists at AVMA disclose that there are a host of vaccines now believed to have little or no efficacy, yet they remain approved and in the market place. Why is this?
   a. Efficacy testing, required by the VST, is codified in 9CFR. This Code of Federal Regulations defines, in many cases, the challenge model used to determine efficacy. In nearly all cases, that challenge occurs very, very soon after the completion of the vaccination protocol. For example, the standard is two weeks post-vaccination. This would be the interval between vaccination and challenge for efficacy studies for the vast majority of vaccines approved.
   b. Efficacy testing requirements can be met with a very small number of animals, usually less than 20. Given the variation in populations and the latitude available to sponsor companies in selection of test animals, relevance to field situations may be oblique at best.
   c. "Efficacy" is a relative term with the actual acceptable outcome being **very** dependent on the type of label sought by the sponsor. For more explanation, please refer to notes on "Labeling".

d. The challenge model, in some cases, is mandated by 9CFR including the challenge strain. In other cases, however, models are proposed by the sponsoring company, approved by CVB and are used to determine the efficacy standards for the product. In those cases, the actual model and the challenge are considered proprietary information and are unavailable to the profession and the public. These are viewed as trade secrets and the companies assert their right to hold in secrecy the details of these challenges. The relevance to efficacy in the field is thus hard to objectively evaluate merely by the CVB approval.

6. How a vaccine is licensed, for example in which category, has great relevance for practitioners. Often they are not aware of the licensing category. Vaccines can have a stamp of approval from CVB in one of three categories:
   a. **Fully approved**. Fully approved biologics that have earned a license have met the standards for PPSC. As such, they are available to be marketed throughout the U.S. unless, for some reason, prohibited by disease eradication or elimination programs in certain regions or through the limitation placed on the license by CVB.
   b. **Conditional licensure**. Conditional licenses are granted by CVB under special circumstances. In such cases, purity, potency, and safety issues must be defined. However, efficacy only needs to be demonstrated as a "reasonable expectation of efficacy". Historically, conditional licenses have allowed products to enter the market, often with stringent requirements attached to them such as marketing or use limited to a small geographic area where the problem exists. There is a time limit on the conditional license by which time it must either raised to the standards required for full licensure or be withdrawn from the market place. Unfortunately, conditional licensure is often severely abused by the profession and the public as well as the sponsoring company, knowing full well that the CVB on its limited budget has little, if any, surveillance and compliance, manpower or funds. The conditional vaccine often spreads rapidly into animals for which it was not indicated and certainly into regions of the country for which it was not approved. The classic "camels nose under the tent", conditional licenses has true limited utility in the effort toward best patient care.
   c. **Autogenous vaccine**. Autogenous vaccines are to be made from an isolate from a specific farm, are driven by the practitioner's determination that fully approved products are ineffective, and there is minimal oversight. Autogenous biologics have requirements for purity and safety similar to those required by the other two categories. At least, this is the paperwork requirement. A great deal of skepticism abounds as to the actual implementation of even these minimal requirements. The much greater point for awareness by all veterinarians is the **lack of any efficacy** requirement and **no potency requirement** for autogenous biologics. In addition there is little regulatory oversight, given the limited resources of the CVB.

7. **Federal Preemption**. On August 27, 1992, the USDA published a Final Rule (57 FR 38758) in the Federal Register that prohibited States from imposing requirements regarding PPSE which differ from USDA. This preemption was aimed at the States and weren't intended to preempt common law actions. That is not how it worked out. Interpretations by courts essentially conclude that a USDA-CVB license is evidence, by its issuance, that a product is PPSE. Effective challenge to PPSE has been rejected by the courts in cases brought by damaged parties, with a number of disturbing outcomes. Not the least of which is a repositioning of the veterinarian as a target of liability actions when losses associated with vaccines arise.
8. **Old or Outdated Antigens**. Lacking any structured system for ongoing field efficacy assessment, adverse reaction data collection or critical review processes, a licensed vaccine may seem to live far beyond its technical value. CAV1 and CAV2 vaccines in the dog would be one such example. Through ignorance of a better product and failure to remove outdated antigens from licenses, a more dangerous antigen may persist in the marketplace.
9. **Label claims**. For practical purposes, three types of efficacy categories (claims) are recognized by CVB. The label claims reflect differing levels of assurance of performance. It is important to read the label, determine the category and to understand just what is required of the biologic company to achieve that claim. It is the prerogative of the company to negotiate the claim they seek with CVB. It should be noted that nearly all swine vaccine labels are **"c)"**.
   a) **Prevents infection**..... most stringent

b) **Prevents disease**..... Recognizes infection occurs but the disease is prevented or attenuated

c) **Aids in the prevention and control of losses associated with**..... Statistical association that vaccination results in less severe clinical signs or production losses as demonstrated by the sponsor's test method

To provide **Best Patient Care** and **Best Service to Clients**, I believe it is imperative that the veterinary profession learn, in detail, the safety, efficacy, liability and economic issues that are driving contemporary vaccine development and marketing. The time is long overdue for critical, on-going end user input into this most important part of our professional activity.