

Vaccine Efficacy and Other Unexpected Consequences

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Abstract

Vaccine efficacy is the obvious objective of the developer, manufacturer, licensing agency and the user. The degree of attainment, and indeed the validity of its confirmation, is very often a tenuous quantity. Expectations of each of the principals vary. Manufacture is economics and business driven and a premium attends simplest measurement and earliest regulatory approval. Government's licensing procedure is constrained to utilize principally the "reasonable" presentation of the manufacture and is neither authorized nor funded to confirm experimental data independently. Users purchase the product as insurance against anticipated disease that may have earlier been misdiagnosed, misunderstood or even iatrogenic. Users perceive efficacy or failure with equal uncertainty. Degree of challenge, unrecognized agent-host-environment interaction, incomplete or failed diagnosis, all may confound even the most curious or dedicated. Unintended consequence of vaccination, including endointoxication, may further obscure understanding of apparent vaccine failure.

Introduction

The unique provision for intrastate biologics production and licensing enjoyed by California provides me opportunity and challenge. Opportunity to work closely with producers and users of veterinary biologics and the challenge to avoid both medical injury and civil liability. I am inclined to believe that if my malpractice carrier had any sort of real understanding of potential problems, I'd never be able to afford his fee.

Both USDA-Biologics and CDFA declare their regulatory objective and reason for existence is the assurance that vaccines and diagnostic reagents be **safe, potent, and efficacious**. And to paraphrase the Biblical citation, "The greatest of these is **efficacy**". There is no other objective in the user's mind and no more determinative requirement for the manufacturer. Vaccines are expected to "work". Any disease event subsequent to vaccination - sometimes even **very** subsequent, brings into doubt the question of "working".

"Efficacy" can be expressed as the degree to which perceived vaccine function fulfills the expectation of the user, developer/manufacturer, and licensing agency. The user's perception is absolutely determinative of the continued presence of the vaccine in the market place.

Efficacy and the User

The user's perception of efficacy based upon:

1. Disease risk estimate and need to avoid loss.
2. Experience with animal disease.
3. Advice from other owners, DVM, University and advertisers.
4. Diagnostic variability in sensitivity/specificity.
5. Variable immune experience in succeeding animal generations.
6. Highly variable environmental challenge.

Vaccination may be usefully described as "insurance". It is an investment by the animal owner in the avoidance of disease loss. Importance of disease avoidance is based upon experience and influenced by the experience of others including the prescribing veterinarian. The continuing credibility of the latter often turns on the owner's perception of efficacy.

The animal owner's understanding of disease risk is usually based upon local experience and information from veterinarians. University Extension programs — and manufacturer's advertisement — contribute to this understanding. Accuracy of diagnostic procedures are obviously critical. We, as well as our clients, are sometimes less than fully aware of the multiple causation of disease. Failure to completely understand interactions between host, parasite, and the environment that actually determine appearance and course of disease leads us all into a premature assumption that agent plus host equals disease. When clinical examination, necropsy, and laboratory analysis lacks adequate sensitivity and specificity, and then when we further degrade the diagnostic process by ignoring the complexity of the disease process, we sometimes fail to identify our real vaccination needs or we inaccurately assess efficacy.

Examples and Discussion

In my opinion, a major contributor to inadequate owner awareness and to error on the part of the practi-

tioner lies in acceptance of a diagnostic laboratory finding of a specific agent or, worse yet, antibody evidence interpreted as agent presence, as a “diagnosis”. Then follows a possibly erroneous selection of vaccines or the belief that an earlier vaccination procedure “didn’t work”.

Of course there is still much to discover regarding disease control through modulation of the immune system. In many circumstances there are also things to learn regarding the natural history of the agent or its pathobiology. When we encourage clients to assess vaccines by their ability to seroconvert, while immunity to certain disease process is actually mediated in other than the humoral system, we need to be cautious of our conclusions — and slow to suggest that potency is proof of efficacy.

Efficacy and the Manufacturer

The manufacturer’s approach to efficacy is conditioned by perceptions of the market-place and regulatory constraints including:

1. Licensing / regulatory requirements.
2. Cost of development / production / distribution.
3. Estimates of competing products including estimates of user confidence, follow-up of reported malfunctions of competing products.
4. Availability of information or availability of research to sustain a new hypothesis.

The veterinary biologics industry employs professionally competent scientists and technicians, is acutely aware of research progress in our universities and only slightly less aware of progress among competitors. When vaccine users perceive a need for a product or when the perception can be created, the production industry will almost certainly respond. That response will include estimates of potential market, position of competing products if any, and opportunity to build upon new or developable technology.

This process takes place with at least an eye on the expectations and requirements of the licensing agency. Those requirements most often follow a simultaneous regulatory estimate of clinical need, current research hypothesis, and an ongoing awareness of competing product performance.

For products with substantial user experience and where there is comprehensive research literature, the Code of Federal Regulations, or CFR, will have already prescribed minimum standards for safety, potency and efficacy. The latter most often employing challenges under conditions that are designed to mimic nature.

For new technology or when the clinical requirement is not fully defined, the licensing agency calls upon the manufacturer to recommend procedures presumed to reasonably mimic nature. These may eventually be

confirmed as reasonable or may require further amendments. Cost and the perception of need among users and their communication with regulatory authorities, contribute to this process.

Clearly, cost and market considerations impact the manufacturer’s estimated need to measure efficacy. Small-numbers trials are very often proposed and procedures to control unrecognized variables sometimes ignored. The latter is especially problematic when the condition is “newly emerging” or the subject of high public concern. Although fiscal considerations may lead a manufacturer to press for minimal regulatory requirements, difficulty often encountered in creating disease among non-vaccinated controls tends to force manufacturers toward more realistic challenge trials. However, both manufacturer and regulator recognize the reality of challenge manipulation in the laboratory environment. Most infectious diseases are not only complex in causation but very dose-dependent. Similarly, immune response may fall anywhere along a continuum from none to too much (hypersensitive).

Even very useful immunogens can be over-challenged and appear to have failed. Conversely, dangerous agents may actually require high doses or other complex determinants to cause disease, and lower doses may be interpreted as evidence of efficacy. Age, sex, sometimes breed, and other characteristics of the trial population may introduce unrecognized variables as well.

The manufacturer then moves to permitted field trials sensitive to both population and seasonal variables and presumably more nearly mimicking nature. Control is often far more difficult in such field trials than in the laboratory. At this point, if controlled trials indicate probability of efficacy, or if local or emergency need is deemed high, limited or preliminary licensure may be granted to permit wider-area application as well as some recovery of trial costs through sales. Such commercial trials can be useful and, in the long run, eventually determine the user’s estimate of efficacy. However, they are rarely contemporaneously controlled and often rely upon comparing results we see this season with observations of earlier periods or differing circumstances.

The manufacturer assumes responsibility for investigation of reports of failure or malfunction. Almost all such complaints from the user are referred by USDA to the manufacturer for resolution. Potential civil liability becomes the important compliance tool.

Efficacy and the Regulator

The licensing agency assesses manufacturer’s claim of efficacy through:

1. Understanding nature of the disease including identification of “case” parameters and other variables.

2. Hypothesized product function (proposed label-claim).
3. Trial design.
4. Analysis of data.
5. Field trials and analysis
6. Very limited follow-on of efficacy and investigation of reported failure or accident.
7. Continuing assessment of quality control procedures.

Availability of efficacious biologic products is the bottom line mission of USDA's Veterinary Services biologic program. Given earlier satisfactory confirmation of safety and the demonstration of some mechanism to prove biologic impact (potency) in the vaccinate, the entire regulatory effort is dedicated to confirming manufacturer's claim of product efficacy and to quality control. Budgetary and legislative restrictions require that most of this be accomplished in pre-licensing effort. Assets for follow-on study are very limited. The regulator tries to "get it right the first time". This can be costly, both fiscally and in terms of time. Trials specified will be based upon earlier CFR requirements or upon acceptance of manufacturer's alternate proposal for novel products. Tug and pull between manufacturer and regulator usually evolve into reasonable requirements for demonstration of efficacy in the laboratory. Time required for this may be long, depending upon novelty of approach or perception of dangers. Manufacturer's costs and risk-perception by the regulator will eventually determine whether qualifying laboratory trials will be undertaken. Usually, compromise is found and field trials undertaken.

The regulator imposes field trial requirements that will control as many variables as possible. This includes compliance with valid case-parameters. Trials are designed to be sensitive to both population and seasonal variables and presumably attempt to mimic nature. Control is almost always more difficult in such trials than in the laboratory. At this point, if the controlled field trials indicate probability of efficacy, and if emergency or local needs justify, limited or preliminary licensure may be granted to permit wider-area application as well as some recovery of trial costs through sales. Such commercial trials can be useful and, in the long run, will eventually determine the user's estimate of efficacy. However, they are rarely contemporaneously controlled and often rely upon comparing results we see this season with observations of earlier periods or differing circumstances.

During the field trial stages, it has been my experience to receive a lot of letters from users attesting to the efficacy of the product. Phrasing and other characteristics of such "sure am good" letters sometimes suggest enthusiastic stimulation by some distributors.

The Federal agency enforces accountability, quality control, and good manufacturing practices through unannounced inspections of manufacturer's facilities, procedures, and records. These inspections are remarkably detailed and comprehensive and simultaneously provide opportunity to improve upon even previously approved outlines of production as well as the correction of potential problem areas. However, it rarely injects itself into follow-on efficacy studies after full licensure. This is perceived to be a function of user-manufacturer interaction and responsibility. Reports of product failure or complaints of accidents made to USDA are normally referred back to the manufacturer for resolution. The much smaller California program requires Animal Health Branch and Diagnostic Laboratory investigation and evaluation. This applies to both USDA licensed products used in California as well as intrastate licensed products.

This provision of California law has provided opportunity to recognize phenomena attendant to hypersensitivity, vaccine interaction, lack of homology between agents used to qualify vaccines and those present in the State, antigen strain variability, the development of integrated vaccine programs in poultry now adopted nationwide, and the importance of endotoxins. Investigation of occasional accidents following use of autogenous bacterins prepared from California isolates early led to our requirement to wash autogenous antigens made in the State to remove free endotoxin but we had no clear understanding of the complex manifestations of intoxication, particularly in the dairy cow and calf, until Dr. Jim Cullor began his developmental work on J-5 *E. coli* bacterin. He has provided us critically needed insight to the pathogenesis and clinical expression of endotoxigenesis including both manufacturing strategies and immunization approaches contributing in a major way to resolving our problems. His work is the subject of other presentations here.

Examples and Discussion

We in California are confident most products qualifying for either USDA or California licensure are safe and efficacious. I do not believe, however, that simple user enthusiasm or survival in the marketplace can always be assumed proof of efficacy. Given that many vaccines are probably incompletely challenged in nature, diagnosis of disease often imprecise or misinterpreted, and suspected malfunctions of product inadequately investigated, it is possible for products of poor efficacy to remain in use.

Improved professional sensitivity to reasons for differing perceptions of efficacy among users, manufacturers, and regulators will minimize this hazard.