4.5 Field Safety

1. Overview

Field safety studies are one component of the safety evaluation required for a product prior to licensure. Field safety trials (FST) according to Veterinary Services Memorandum (VSM 800.204) are typically uncontrolled, loosely exploratory trials conducted under typical field husbandry (i.e., intended use) conditions. The objective of a FST is to assess the safety of the product in its target population under the conditions of its intended use. It is intended to detect the types of adverse events which may occur with sufficient frequency to be seen in a trial of this scale. The FST is an essential clinical component of the prelicense process, supplementing smaller preclinical experimental studies, but it does not replace ongoing post-marketing surveillance.

While FSTs conducted as per VSM 800.204 satisfy the safety requirements for most products, there are times when other types of more rigorous field safety studies may be necessary. Such studies generally need the usual features of any designed study and should follow the guidance for study design in documents such as VSM 800.200 and VSM 800.202. For example, most studies of reproductive performance with PRRS MLV vaccines have been well designed and followed a specific analysis.

2. Related Documents

- VSM 800.50: Basic License Requirements and Guidelines for Submission of Materials in Support of Licensure
- VSM 800.67--Shipment of Experimental Veterinary Biological Products
- VSM 800.204--General Licensing Considerations: Field Safety Studies
- VSM 800.211 Licensing Considerations: Vaccine Claims for Protection of the Fetus Against Bovine Virus Diarrhea Virus

3. Procedures

3.1 Permission to conduct a field study must be obtained from the Center for Veterinary Biologics. See the Reviewer Manual Chapter titled “Shipping Experimental Product under 9CFR 103.3,” and VS Memoranda 800.50 and 800.67, for details.

3.2 Applicants are strongly encouraged to submit a detailed protocol for review and comment prior to conducting a study. See the Reviewer Manual chapter titled “Study Protocols” for additional detail.

3.3 If the product to be tested is biotechnology derived, a risk assessment must be completed prior to authorizing a field release. The CVB also may elect to conduct a risk assessment on certain conventional modified live products; contact the Risk Manager in these cases. For certain types of products, a notice of intent to conduct the study must be published in the

Federal Register. See VS Memoranda 800.50 and 800.205, and the Reviewer Manual chapter titled "Summary Information Format (SIF) and Risk Analyses," for additional detail.

3.4 Field safety studies should be authorized only after product efficacy has been adequately demonstrated. Exceptions must be cleared by the Section Leader.

3.4.1 If a field safety study is conducted prior to acceptance of pivotal efficacy data (or "reasonable expectation" efficacy data for conditional licenses), the firm must provide clearly worded efficacy disclaimers to each participating animal owner (see Section 4.4 for details). In such cases, the reviewer must notify the firm that the study is being undertaken at their own risk; should the product subsequently be deemed insufficiently efficacious, the firm is required to notify each participating animal owner.

3.4.2 Field safety studies are never to be authorized prior to adequate demonstration of efficacy for rabies vaccines.

3.4.3 When the product contains live organisms, studies demonstrating a lack of reversion to virulence (aka backpassage) also should be completed prior to authorizing a field study. See VS Memorandum 800.201 for details on backpassage studies.

3.4.4 Acceptable inactivation (including inactivation kinetics) must be demonstrated for killed products prior to authorizing field studies.

3.4.5 Serials used in field safety studies must be tested according to Section V of the Outline of Production, using assays acceptable to the CVB. The firm conducts the study at its own risk if they use serials in the study that have not yet been tested with an approved potency test. Even in such cases, some type of potency testing should be completed prior to study initiation.

3.4.6 Firms often use prelicense serials in field safety studies, but this is not a requirement. If they do not use prelicense serials, the serials still must be typical of the manufacturing process described in the Outline of Production, and they should be submitted to the CVB for confirmatory testing to verify potency.

3.4.7 Generally, studies in broiler birds are followed to slaughter with slaughter data on condemnations reported. Depending on the disease, these studies may serve as field safety studies, as well as provide an indicator of field efficacy [redacted] If a disease lesion (preventable by the vaccine) would cause condemnation, it should be reported separately from the total number of carcasses condemned (for example E. coli product/air sacculitis condemnations or Marek's product/tumor formation). Layer birds are followed for a similar time period as broiler birds but no condemnation data are required.

Review of field safety study protocols

General guidance regarding protocol review is found in the Reviewer Manual Chapter titled "Study Protocols." Specific guidance regarding the content of a field safety study protocol is found in VS Memorandum 800.204. *Additional* items to consider:

4.1 Geographical regions: VS Memo 800.204 states that the study should be conducted in at least 3 distinct geographical regions.

4.1.1 This often leads to questions regarding what is "distinct." A good example might include swine herds from North Carolina (eastern states), Minnesota (upper midwest) and Arkansas (southern mid-states region). An unacceptable distribution might include 2 beef cattle feedlots in the Texas panhandle region and a third feedlot 30 miles across the border in Oklahoma. The acceptability of any proposed combination of sites is left to reviewer discretion and must take into account the individual circumstances regarding animal availability and proposed product use.

4.1.2 The CVB will allow data from a VICH member country (European Union or Japan) to satisfy requirements for *one* of the geographic regions, provided that the data are considered to be applicable to animal breeds and husbandry conditions found in the U.S. and the data are generated in a credible, well-documented study.

[redacted]

[redacted]

4.2.6 Products considered for conditional licensure: A full field safety study is required. Abbreviated requirements for conditional licensure apply only to efficacy and potency.

4.2.7 Colostrum products: [redacted]

4.3 Type/quality of evaluation

4.3.1 The quality and credibility of any field study depends on adequate pre-study instruction for cooperators and clear, complete data capture forms. The protocol should include information regarding how cooperators will be trained and should provide copies of the data capture forms. Data forms should provide a means to confirm:

4.3.1.1 Product administration to each uniquely identified animal (or poultry/aquaculture group). Should include date(s) of administration and identity of personnel involved.

4.3.1.2 Post-administration observations for *each* animal enrolled in the study. This means that normal observations, as well as adverse events, are documented. Forms that capture information only for animals with adverse events are not sufficient; no assumptions should be made regarding animals for which there are no data.

4.3.1.3 Categorization of adverse events according to VEDDRA classifications. This standardized method of reporting facilitates comparisons among different studies and standardizes summary information provided to the public via e-FOIA.

4.3.1.4 The magnitude of the adverse event, if the event has a quantitative component to it (e.g., size of swelling at vaccination site)

4.3.1.5 The duration of the adverse event.

4.3.2 Observations should be made by independent cooperators, not individuals with a vested interest in the outcome (i.e., firm personnel).

4.3.3 Observations at critical periods must be made by veterinarians or trained specialists. This includes initial administration and *at least* one direct follow-up evaluation. Phone calls to owners as the sole means of follow-up are insufficient.

4.3.4 Intermediate observations may be made by caretakers or animal owners, provided that they are given adequate, specific instructions *and* forms to document observations. Data forms filled out by lay personnel should be actively collected by the study

cooperator from each lay participant (i.e., Don't rely on passive submission of completed forms, assuming everything is OK if the owner doesn't return the forms.)

4.3.5 It is common for the reported adverse event rate to vary substantially among cooperators. In many cases, this is due to differences in reporting. (Example: One cooperator may be very diligent in reporting every small, transient swelling. Another may consider such swellings to be a "normal" consequence of vaccination and will not note anything on the data form.)

This variation can be minimized by adequate training of all cooperators. Firms are responsible for clarifying to cooperators that ALL sequelae, regardless of magnitude or duration, should be reported. The clinical relevance of the events will be determined during data analysis; data should not be censored at the cooperator level.

Firms should not pool data from different sites in the final report. If there are material site differences, adverse event rates should be described as a range of the individual site values rather than an average value.

4.4 Informed consent forms: Animal owners should always be notified that an experimental product is being used; to this end, most firms will provide some kind of informed consent form. In special situations where the field safety study is being performed before pivotal efficacy has been demonstrated (see Section 3.4), a specific informed consent form is required. Similarly, if confirmatory testing of prelicensing serials by the CVB is not yet completed, specific pre-approved disclaimers may be required. Firms should provide a copy of the informed consent form for CVB review with the study protocol, and it is the responsibility of the reviewer to ensure that the form adequately and prominently discloses the efficacy status of the product. (Avoid forms that attempt to downplay the significance of the undetermined efficacy and/or hide this disclosure in small print.)

4.5 The use of beta-adrenergic agonists in feedlot cattle or feeder pigs concurrent with the vaccination-observation period of the study: Beta agonists such as Optaflexx™, PayLean™, and Zilmax™ are sometimes used in feedlot cattle and feeder pigs to increase lean slaughter weight; these products are typically used the last 30 days of feeding. The CVB will not accept data from field safety studies when these drugs are used concurrently with vaccination as use of these drugs can mask and/or cause adverse effects, and normally are not administered at the same time as vaccination.

4.6 Inconsistent test results (between the firm and confirmatory testing at the CVB): If results obtained during confirmatory testing call product safety into question, the CVB laboratory may conduct small scale studies with prelicensing serials to further evaluate product safety prior to authorization of field safety studies.

5. Review of Field Safety Study Reports

5.1 Statistics Review

Most field safety studies involve only simple descriptive summaries, rather than inferential statistical methods. Thus, many field safety submissions do not require lengthy statistical analysis. [redacted]

[redacted]

[redacted]

[redacted]

5.2 CVB Response

5.2.1 CVB response letters should specify any label warnings that may be required as a result of field safety study findings.

5.2.2 Send a cc: of the response letter, as well as a copy of the incoming submission, to the CVB Epidemiologist.