



VS Memorandum 800.126

Efficacy and Safety Studies for Cancer Immunotherapeutics

1. Purpose and Background

This memorandum provides guidance on conducting safety and efficacy studies for cancer immunotherapeutics. This Veterinary Services Memorandum (VSM) supplements existing Center for Veterinary Biologics (CVB) guidelines: including VSM [800.200](#), General Licensing Considerations: Study Practices and Documentation, VSM [800.202](#), General Licensing Considerations: Efficacy Studies for Prophylactic and Therapeutic Biologics; VSM [800.301](#), Good Clinical Practice; VSM [800.207](#), General Licensing Considerations: Target Animal Safety (TAS) Studies Prior to Product Licensure - VICH Guideline 44; and VSM [800.121](#), Autologous Therapeutic Biologics.

Cancer immunotherapies are used in the treatment of animals diagnosed with cancer, as opposed to conventional vaccines, which are administered to healthy animals to prevent infectious disease. This difference and the heterogeneity of naturally occurring neoplastic disease requires unique safety and efficacy studies when evaluating immunomodulatory cancer products, unlike safety and efficacy studies used in evaluating biologics used for infectious agents. CVB's intention is to address these fundamental differences by establishing requirements for demonstrating safety and efficacy for these products. The design of these studies, the acceptable level of risk of adverse events, and the standard for efficacy must balance the benefits versus the risks to the patients. This risk is compounded by the necessity of using client-owned animals, with naturally occurring disease, to determine efficacy during early product development. The guidance in this memo applies to the evaluation of biologics that are cancer immunotherapeutics used to treat neoplastic disease, including autologous immunotherapeutics. CVB expects that aspects of the guidance will also apply to immunomodulatory products for non-neoplastic disease that involve client-owned animal studies in product development.

Pursuant to the Congressional Review Act (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as a non-major rule, as defined by 5 U.S.C. § 804(2).

2. Document Status

- A. Issue Date: 09/02/2020.
- B. This is a new document.

3. Authority and References

A. Authorities



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[7 CFR 371.4](#)

[9 CFR 101.2](#)

[9 CFR 102.6](#)

[9 CFR 103.3](#)

[9 CFR 116.9](#)

B. References

- 1) [VICH Guideline \(GL\) 43](#) (Target Animal Safety for Veterinary Pharmaceutical Products)
- 2) [VSM 800.121](#), Autologous Therapeutic Biologics
- 3) [VSM 800.200](#), General Licensing Considerations: Study Practices and Documentation
- 4) [VSM 800.202](#), General Licensing Considerations: Efficacy Studies for Prophylactic and Therapeutic Biologics
- 5) [VSM 800.204](#), General Licensing Considerations: Field Safety Studies
- 6) [VSM 800.205](#), General Licensing Considerations: Biotechnology-derived Veterinary Biologics Categories I, II, and III
- 7) [VSM 800.207](#), General Licensing Considerations: Target Animal Safety (TAS) Studies Prior to Product Licensure
- 8) [VSM 800.301](#), Good Clinical Practice

4. Audience

VS employees and members of the biologics industry.

5. Guidance

The applicant must design strategically focused studies that demonstrate efficacy and safety within a specific species against a single tumor type or specific biomarker. For all cancer products, CVB will usually require an investigator to first conduct preliminary studies and then pursue conditional licensure prior to proceeding to full licensure.

A. Preliminary Studies Required Prior to Performing Pivotal Combined Safety and Efficacy Studies

The applicant must demonstrate that the product is supported by scientifically sound theory and that the risks of using the product outside the laboratory in client-owned animals are addressed prior to performing pivotal safety and efficacy studies in client-owned animals for conditional licensure. Data necessary to address these requirements can be obtained through small pilot studies, related previously conducted studies, and peer-reviewed publications involving research animals and client-owned animals. CVB acceptance of these small-scale, preliminary studies is



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needed before pivotal studies would be allowed in client-owned animals, but does not imply that the normal licensure requirements for these issues are met.

1) *Supportive Studies*

The applicant should submit any studies, including the supporting data, completed prior to the pre-licensing process or performed in other species that model the mode of action, for consideration as supportive evidence in the evaluation of safety, efficacy, mechanism of action, and environmental risk assessments. CVB values comparative oncology research because of its potential to advance both veterinary and human immunotherapies. Applicable studies used in the development of human products that have been previously reviewed and approved by other Federal agencies have the potential to meet CVB requirements.

2) *Environmental Release and User Safety Studies*

Prior to performing any studies outside the laboratory, the applicant should address risks to the environment or to user safety caused by inadvertent human exposure to the product. The applicant will evaluate the risks and any necessary control measures needed to limit human exposure to the product during the product administration or care of the animal after treatment. The procedure for evaluating these potential risks is in VSM [800.205](#), General Licensing Considerations: Biotechnology-derived Veterinary Biologics Categories I, II, and III.

3) *Demonstration of Proof of Concept in Target Species*

Prior to performing pivotal combined safety and efficacy studies, CVB expects the applicant to have demonstrated a defined mechanism of action or have demonstrated an immune response likely to provide an anti-neoplastic effect with the product. This product-specific data should be supported by scientifically sound theory. These studies exploring the mechanisms of action are necessary for the applicant to properly design future combined safety and efficacy studies. Either in vitro studies or in vivo pilot studies can be used to demonstrate the mechanism of action in the target species. Product-specific, in vivo studies may be done either prior to, or as part of, conditional licensure efficacy studies in client-owned animals with adequate justification. For example, if the applicant has a product with a mechanism of action that targets and depletes a specific cell type, then the investigator's analysis of the study should confirm an immune response and/or depletion of that cell type in vivo in the target species. This type of study is integral to any scientifically sound product development plan.



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4) *Safety Studies*

CVB establishes safety study requirements for each product dependent upon the expected adverse events, based on similarly classified immunotherapeutics and the optimal methods to identify adverse events. While CVB expects there will be minimal adverse reactions with some cancer immunotherapeutics, there may be consequential unforeseen adverse reactions with other products. CVB encourages firms to submit safety study protocols for review for suitability prior to beginning the study and to supply relevant safety study references describing existing human or animal products that act by a similar mechanism as the proposed product. The applicant should provide previously generated safety data, as applicable and specific to the experimental product, to CVB for evaluation. Prior to conducting pivotal studies, the applicant should complete an initial target animal safety study, followed by acquisition of additional safety data later in the licensing process. This is recommended to identify potential adverse events prior to using the therapy in large numbers of client-owned animals necessary for a pivotal study.

- a. If the applicant can provide safety data from pilot studies in client-owned animals that meet the intent of this requirement, the target animal safety testing study using research animals may be postponed until later in the licensing process. Additionally, some products, such as autologous cancer products, may be allowed to use alternative study designs using only client-owned animals if the study design meets the intent of this requirement.
- b. For the target animal safety study, the applicant is generally required to administer the product at or above the normal dosage following the normal treatment schedule to a minimum of eight (8) target species animals. CVB generally requires such studies to last a minimum of two (2) months after initiating therapy. CVB requires physical examinations and daily observations for acute reactions, hematology, serum biochemistry, and urinalysis at appropriate intervals. The investigator is not required to include negative control animals in the study and is only required to perform postmortem examinations of the study animals if adverse events or abnormal laboratory test results warrant further investigation. Investigators should follow the guidance in VSM [800.207](#) for general aspects of study design.
- c. Describe and report adverse events identified in these safety studies using the published Veterinary Cooperative Oncology Group (VCOG) consensus document on common terminology for adverse events.¹
- d. If CVB determines that the initial safety data is satisfactory, then CVB may allow the investigator to perform pivotal combined efficacy and safety



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studies in client-owned animals with neoplastic disease.

5) *Pilot Efficacy Studies*

CVB may allow pilot efficacy studies following title 9, *Code of Federal Regulations* (9 CFR) part [103.3](#) on multiple tumor types in multiple species to broadly evaluate the product for evidence of efficacy and safety. The goal of these pilot studies is to determine all the necessary conditions to design and run an informed pivotal safety and efficacy study. The applicant should use pilot studies to identify additional safety information and to determine how the product will be used, including determining labeling for specific tumor types, species, dose, and treatment schedules.

B. Combined Pivotal Field Efficacy and Safety Study Considerations for Conditional Licensure

CVB requires applicants to design a pivotal study to demonstrate a reasonable expectation of efficacy and an acceptable safety profile based on the information acquired from the preliminary studies described in Section 5.A. The pivotal study data will be used to support and obtain an initial, conditional license, generally a required step prior to obtaining full licensure for cancer immunotherapeutics. The eligibility to obtain a conditional license will follow 9 CFR [102.6](#), but CVB recognizes that neoplastic disease is very heterogeneous, even within a single tumor type, and curative biologic therapies are rarely available.

Applicants should use a study design and practices that broadly follow the guidance in VSM [800.202](#), General Licensing Considerations: Efficacy Studies for Prophylactic and Therapeutic Biologics; and VSM [800.301](#), Good Clinical Practice. Some of the guidance in those documents is aimed at studies based on exposure to an infectious pathogen and the applicant should propose modifications to those features to better suit the evaluation of an immunotherapeutic treatment for spontaneously occurring disease. CVB recommends submitting a protocol for review well in advance of initiating these complex studies. Additionally, the protocol should include a method to evaluate patient quality of life into the study design to develop supportive information for the product.

The ideal efficacy study evaluates overall survival; however, CVB may allow studies using surrogate endpoints. Surrogate endpoints allowed by CVB include disease/event-free survival, progression-free survival, time to progression, and objective response rates. CVB may also consider other alternative study end points, as well as rigorous adaptive trial designs. Studies using multi-agent therapy must also follow the guidance within Section 5.D. All studies should follow the “intention to



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treat principle” to avoid inappropriately excluding animals enrolled into the study from the analysis.

Both longitudinal studies and objective response studies are acceptable methods to demonstrate efficacy for conditional licensure. Specific requirements for these two (2) common efficacy study designs and the requirements for the concurrent safety component of these studies are listed below.

1) *General Requirements for Longitudinal Efficacy Studies*

- a. Longitudinal studies are those tracking time-based endpoints, such as overall survival, progression-free survival, and time to progression. CVB requires such studies to be prospective, at least double-armed, randomized, and blinded. Patient selection and stratification must be done on prognostic indicators demonstrated to have a predictive value for both treatment and control groups. The applicant must fully describe and justify criteria for inclusion or exclusion of patients from the study. Each patient should have a well-characterized tumor type diagnosis using appropriate diagnostic methods. Include other relevant prognostic factors, such as tumor subtype, tumor grading, clinical staging, and previous or concomitant therapies, in the final report even if these factors were not used for patient selection or stratification. The control group should receive an ethically and clinically appropriate therapy or placebo. For example, an acceptable study design might compare a treatment group that receives the experimental immunotherapy plus the standard of care therapy against a control group that only receives the standard care therapy.
- b. For studies with rolling enrollment, CVB recommends randomization within sequential blocks of subjects (permuted block randomization). Block size should be a multiple (e.g., one time (1x) or two times (2x)) of the number of treatment groups. CVB prefers a two times (2x) multiple block size to diminish the possibility of spontaneous unblinding, but this may be logistically infeasible if enrollment at individual sites is expected to be low. Applicants must stratify randomization on major prognostic indicators demonstrated to have a predictive value for the specific tumor type and species in the study. Each enrollment site should have its own randomization schedule, which can be maintained either locally or by a central offsite authority. The use of slightly unequal numbers of animals in the treatment and control groups, up to a two-to-one (2:1) ratio, would generally be acceptable.
- c. CVB will consider variations on the standard longitudinal study design shown above (5.B.1.b) if CVB determines that the proposals are statistically sound and there is strong justification for the alternative study design. Because the



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study design variations shown below may weaken the study results, the applicant should design the study to account for the additional uncertainty caused by these variations. Examples of alternatives to the standard study design that may be considered are:

- i. Use of data from a non-randomized, concurrent, prospectively selected, matched population of animals receiving standard of care therapy by board-certified oncologists at a minimum of three (3) specialty hospitals as the control group. The control group in this study design would be less effective than the use of a randomized and blinded control group.
- ii. CVB discourages use of historical data as a comparator to a treatment group. CVB discourages investigators from using this study type because there are proven disadvantages to using historical data when examining progression-free survival or overall survival. CVB may consider allowing this under very limited and specific circumstances for conditional licensure, but not for full licensure. CVB may allow use when the historical data from multiple sources with similar study designs and study populations all demonstrate that disease progression and response to the current standard of care is well characterized and consistent.
- iii. CVB recognizes that blinding may not be feasible for all therapies and will consider alternative study designs in these unique circumstances.

2) *General Requirements for Objective Response Efficacy Studies*

Objective response studies are single arm, non-randomized, non-blinded studies which objectively measure responses, such as a decrease in tumor size or volume. CVB may consider other measurable responses, such as a decrease in circulating neoplastic cells, as meaningful objective responses if they are both well recognized and highly clinically relevant. CVB requires such studies to enroll animals that will be observed for a minimum of four (4) months after treatment, so that preliminary temporal data on disease progression or survival are also collected. The applicant should follow study design and tumor response evaluation guidance described by nationally or internationally recognized organizations, such as the VCOG consensus document on response evaluation criteria for solid tumors or the Response Evaluation Criteria in Solid Tumours (iRECIST) guidelines for immunotherapeutics.^{2,3} The investigator must blind clinicians to previously recorded measurements at the time of each assessment. Documenting measurements via digital imaging is generally recommended and representative images should be included in the final report as appropriate.

3) *Safety Evaluation and Adverse Event Reporting for Conditional Licensure*



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The applicant must design both longitudinal and objective response rate efficacy studies to concurrently evaluate product safety. Design the safety monitoring portions of the study to fully identify and evaluate any adverse events (AE). Perform observations for both subclinical and clinical adverse events through physical examinations, hematology, serum biochemistry, and other appropriate methods at regular intervals.

- a. The applicant should generally follow the applicable sections of VSM [800.204](#), General Licensing Considerations: Field Safety Studies, for identifying AEs in companion animals, assessing the relationship of the AE to the product, and the AE reporting requirements, unless otherwise noted below.
- b. The firm must describe and report adverse events following the VCOG consensus document on common terminology for adverse events.¹
- c. Perform complete postmortem examinations, including histopathology, on available patients that die during the trial to evaluate subclinical/clinical AEs and to define the level of disease progression at the time of death. At a minimum, perform postmortem examinations on patients for which the cause of death is unclear or there are significant subclinical or clinical abnormalities not clearly attributable to an identified cause before death. Thorough and timely antemortem evaluations of patients using diagnostic imaging and other examinations to assess both the cancer status and overall health of the patients may be an acceptable replacement for postmortem examinations in appropriate circumstances, such as when an owner does not allow a postmortem examination.

C. Combined Efficacy and Safety Study Design Considerations for Full Licensure

The applicant should design full licensure studies that will demonstrate product efficacy and safety in a larger population of patients than was required for conditional licensure. The study should reflect the product's planned clinical use, so that the benefits and risks of the product are fully understood. This larger group of patients may expose additional adverse responses, which will require developing corrective measures prior to full licensure and widespread use of the product.

1) *Efficacy Study Designs for Full Licensure*

Efficacy study designs to support full licensure should generally follow the guidance for conditional licensure, but their design and analysis must be fully pre-specified in explicit detail. The firm should submit a protocol and consider CVB's response before beginning the study. Typically, greater numbers of subject animals are expected in studies supporting full licensure than for conditional licensure. When appropriate, a well-designed conditional licensure



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study could potentially expand enrollment to meet the requirements of full licensure, if the study designs in both the conditional and full licensure studies are complementary. Submission of a single protocol for both conditional and full licensure may be allowed, but it should be recognized that information learned during the condition licensure study may require changes to the full licensure protocol.

- a. CVB allows surrogate endpoints in place of overall survival as the primary variable, as described for conditional licensure. However, all studies must include a measurement of the duration of the effect by the immunotherapy in the treatment group compared to the control group as a primary variable. For example, while an objective response study alone may be acceptable for conditional licensure, full licensure would require efficacy be evaluated both by objective responses and progression-free survival endpoints.
 - b. CVB expects that overall survival will be a secondary variable for determining efficacy.
 - c. CVB allows studies using multi-agent therapy if they follow the guidance within Section 5.D.
 - d. All studies should follow the “intention to treat principle” to avoid inappropriately excluding animals enrolled into the study from the analysis. CVB may consider additional analysis methods based on a “per protocol” selection of patients supported by strong justification.
 - e. The applicant should include methods to evaluate quality of life for the patient in the study design; however, CVB will only consider these results as supportive data. Subjective or semi-quantitative evaluations of quality of life should use appropriate blinding when possible.
- 2) *Safety Evaluations and Adverse Event Reporting for Full Licensure*

The applicant must design efficacy studies for full licensure to concurrently evaluate product safety. Monitoring, evaluation, and reporting of AEs associated with the product from only animals enrolled in the pivotal study should generally follow the guidance for conditional licensure studies. However, safety evaluations should be updated to account for any AE findings uncovered during the previous conditional license study.

Properly designed combined efficacy and safety studies in client-owned animals that well characterize the AEs of the product may negate the need for additional pre-licensing safety studies in healthy research animals. This will be determined based on the adverse events observed, and how thoroughly the patients were monitored for both clinical and subclinical adverse events. If the



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AEs from the product are not well characterized during efficacy studies in client-owned animals, investigators will be required to perform additional safety studies in the target species using healthy research animals. These studies in healthy research animals would follow [VICH GL43](#) (Target Animal Safety for Veterinary Pharmaceutical Products) or other approved study designs.

D. Evaluation of Efficacy and Safety When Used as Part of a Multi-Therapy Treatment Regimen

The applicant must provide CVB with rationales that address the issues listed below:

- 1) The study design must demonstrate and distinguish the positive and negative effects of the experimental biologic from the other concomitant therapies through the use of appropriate control groups or other methods.
- 2) There is strong justification for the use of each concurrent therapy or drug.
- 3) The concurrent therapies proposed are broadly recognized and widely used in the specific clinical setting described in the study.
- 4) The therapeutic effects and side effects are well understood and documented for the concomitant treatment regimen.
- 5) The treatment protocols' concurrent surgical, radiological, or chemotherapies are well defined and standardized within the study.
- 6) Use of the concurrent therapies in the target species does not violate regulations from other Federal agencies.
- 7) CVB expects product labeling to fully define the multi-therapy treatment regimen used in the pivotal studies.
- 8) No endorsement of efficacy or safety is made of the concurrent therapies in labeling.

E. Licensure Pathway

In general, CVB requires cancer immunotherapies to be conditionally licensed for a period of time prior to progressing to full licensure. CVB re-evaluates conditionally licensed products for safety, efficacy, and progression toward full licensure at least every two (2) years. If CVB determines that the product continues to have an acceptable level of safety and the firm has made progress toward full licensure, then CVB reissues the conditional license for an additional two (2) years.

- 1) The firm is generally expected to meet CVB requirements to obtain a full



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license within six (6) years of first achieving conditional licensure. CVB may consider extending conditional licensure beyond six (6) years if the firm is developing a therapy for a type of cancer with low prevalence and demonstrates meaningful progress toward licensure.

- 2) CVB subjects conditionally and fully licensed products to normal post- licensure AE monitoring and reporting under 9 CFR [116.9](#), or as otherwise required by CVB. However, as licensed products are used on a larger population of animals, the likely need to refine product label warnings based on AE reporting will be more common in cancer immunotherapies than with conventional infectious agent vaccines. CVB requires the firm to carefully monitor the product for AEs, including lack of efficacy in subpopulations of patients, as defined in 9 CFR [101.2](#). Firms must be in close communication with CVB, so that any AE can be rapidly addressed as required under 9 CFR [116.9](#).
- 3) Reporting and product label warnings of AEs will be categorized based on the stage of licensure and the source of the AE.
 - a. Report AEs identified during the pivotal conditional licensure study to CVB as part of the final combined efficacy and study report. The firm must describe and report adverse events following the VCOG consensus document on common terminology for adverse events.¹ These AEs will be the basis for the labeling warnings and the safety Individual Study Summary (ISS) for the conditionally licensed product. Only AEs that are reasonably associated with the product as determined by CVB will be required to be on product labeling and these events will be termed “adverse reactions” on product labeling to distinguish them from the more broadly defined term of “adverse events.” All AEs will be required to be placed in the ISS. The AEs listed in the ISS can be accompanied by an explanation such as: “Adverse Event: Any unfavorable and unintended event that occurs after the use of the product, whether the cause of the adverse event is known to be attributed to the product or is not attributed to the product, such as pre-existing disease.”
 - b. Spontaneously reported AEs obtained from product use in animals not enrolled in pivotal studies should be reported separately from AEs observed in pivotal studies. This reporting should follow 9 CFR [116.9](#) regulations. Additionally, CVB requires an annual safety report describing all spontaneously reported AEs, using the Veterinary Dictionary for Drug Related Affairs, or VeDDRA, terminology and assigning causality following the ABON system during conditional licensure and for the first two (2) years of full licensure. This annual report is in addition to the normal AE reporting requirements. If necessary, AEs identified through spontaneous reporting may be added to the label warnings. The label text distinguishes these



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spontaneously reported AEs from those identified in pivotal studies.

- c. AEs identified in animals enrolled in the pivotal combined efficacy and safety study for full licensure will be addressed as is described for the pivotal conditional licensure study AE.

6. Citations

- 1) Veterinary cooperative oncology group - common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol*. 2016 Dec; 14(4):417-446.
- 2) Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol*. 2015 Sep; 13(3):176-83.
- 3) Seymour L, Bogaerts J, Perrone A, Ford R, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017 Mar; 18:e143-e152.

7. Implementation/Applicability

Updated policy in this memorandum is effective immediately.