



Animal and Plant
Health Inspection
Service

Veterinary Services

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VETERINARY SERVICES MEMORANDUM NO. 800.200

TO: Veterinary Services Leadership Team
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

FROM: John R. Clifford /s/ *John R. Clifford*
Deputy Administrator

SUBJECT: General Licensing Consideration: Study Practices and Documentation

I. PURPOSE

This memorandum provides guidance to licensees, permittees, and applicants concerning the submission of documents to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale, according to title 9, *Code of Federal Regulations* (9 CFR), sections 102.5 and 104.5.

II. REPLACEMENT

This memorandum replaces Veterinary Services (VS) Memorandum No. 800.200 dated June 14, 2002.

III. BACKGROUND

A. Licensing Considerations

Licensing considerations provide guidance to applicants concerning material submitted in support of license applications. They assist the Center for Veterinary Biologics-Policy, Evaluation, and Licensing (CVB-PEL) in maintaining uniformity and consistency in the review of license applications. General licensing considerations address basic principles that have general application in the licensing of products.

B. Study Practices

This memorandum includes general guidance for designing and conducting studies supporting all aspects of product license applications. It focuses on the preparation of technical documents and records.

C. Related References

Details for particular types of studies may be found in other CVB General Licensing Considerations, published in VS memorandums. Guidance also may be found in internationally harmonized guidelines generated through the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH; <http://www.vichsec.org>).

IV. GUIDELINES

General Licensing Considerations: Study Practices and Documentation is appended to this memorandum.

V. IMPLEMENTATION/APPLICABILITY

This revised memorandum is effective immediately and applies to all regulatory study submissions.

Appendix

Appendix

General Licensing Considerations: Study Practices and Documentation

1. Introduction

1.1 *Aim.* This guidance includes general principles for technical documents and data from studies supporting various aspects of a license application.

1.2 *Required documents.* Completely document each phase of the study. Capture the study's progress, and include at least the following:

<i>Document</i>	<i>Phase</i>
protocol	design
records	implementation
statistical package	data analysis
report	presentation

1.3 *Type of study.* Among the types of studies undertaken to support a product's approval may be those which are clinical or nonclinical, experimental or observational, and exploratory or confirmatory. Exploratory studies are aimed at elucidating general or specific features of the material or process under investigation, such as its anticipated performance under various conditions, the feasibility of particular applications, or the optimization of certain procedures. Confirmatory studies are those undertaken to support final production or testing specifications or specific label statements.

1.4 *Biological product.* A biological product is defined by its intended use, and a product's intended use is indicated by the claims made on the label and other product literature (9 CFR 101.2(1)). Consequently, include proposed claims, indications, and cautions in protocols and reports of confirmatory efficacy and safety studies.

1.5 *Scientific standards.* Design, conduct, analyze, and report the study according to sound scientific principles. Follow accepted standards for objectivity and scientific rigor in all studies, and reflect those standards in documents associated with those studies.

1.6 *Statistical principles.* Apply appropriate statistical principles at all stages of development, from conceiving the initial research question, through study design, analysis and interpretation, and culminating with the presentation of the results in the final report. This usually entails ongoing interaction between the responsible statistician and other study personnel.

2. Protocol.

2.1 *Purpose.* The study protocol is a comprehensive document outlining the proposed study. It states the objectives, describes the design, serves as a plan for the execution and analysis, and specifies the conclusion criteria.

2.2 *Submission.* At least 60 days before beginning a study, submit a protocol to the CVB-PEL for review. CVB-PEL may comment on the protocol or recommend its revision if there appear to be serious design flaws that could preclude the possibility of a valid study. Seek CVB concurrence on a confirmatory study before initiating work. Such concurrence, however, does not necessarily imply blanket approval of all possible realizations of the study's conduct or outcome.

2.3 *Content.* Include the following information in a protocol:

2.3.1 *Objective.* Explicitly state the objective of the study. Differentiate between an exploratory and confirmatory study. For a confirmatory efficacy studies, state the proposed label claim(s). Ensure the objective is consistent with the type of study and its context in the product's development. Ensure the protocol answers a relevant research question. The objective of an exploratory study may be broadly stated and open ended, but ensure the objective of a confirmatory study is specific, explicitly stated, and aimed to support any applicable label statements.

2.3.2 *Background.* Give background information justifying the proposed study, placing it in the context of the product's development, and supporting an understanding of its objective. Include a summary of all similar studies previously initiated with the current product or related products and a description of other relevant information. If prior studies were submitted for regulatory review, include the assigned CVB Mail Log numbers.

2.3.3 *Personnel.* Identify the personnel principally responsible for overseeing the study, such as the principal investigator, monitor, cooperators, responsible clinical and laboratory personnel, and statistician. If necessary, state the role played by those not directly engaged by the study, such as animal owners or farm employees. List all study locations.

2.3.4 *Sequence of events.* State the proposed sequence of critical events and, if known, approximate dates. The CVB, at its discretion, may elect to observe critical animal study events, such as vaccination, challenge, and clinical outcomes.

2.3.5 *Materials.* Provide detailed formulations of the experimental products and the results of any tests conducted on them. Describe other essential materials or reagents. For clinical trials, describe the nature of the placebo or active control treatment.

2.3.6 Design considerations. Ensure the study design takes into account the type of study and its objective, as well as relevant scientific features and pragmatic concerns. Aim to reduce bias, increase precision, and estimate error.

Some important considerations for clinical trials include:

2.3.6.1 Experimental Unit. Identify the experimental unit. The experimental unit is the smallest unit which may be randomly assigned to a distinct treatment. In some studies, this may differ from the study unit at which outcomes are measured. If these differ, specify both. For example, in a study of passive immunity, the experimental unit is the sow, but the outcome unit is the piglet suckling the sow.

2.3.6.1.1 State the number of experimental units, and indicate whether there is more than one level of replication.

2.3.6.1.2 Describe the selection of the experimental units and criteria for inclusion or exclusion.

2.3.6.1.3 In studies utilizing live subjects, describe the nature and source of the subjects and their relationship to the target population. State how they will be identified, grouped, housed, and commingled.

2.3.6.2 Randomization. Describe the randomization plan as well as the method of randomized treatment allocation or sample selection. Include, for example, the scheme for blocking or stratification.

2.3.6.3 Housing. Provide a detailed description of animal housing arrangements during each phase of the study. If helpful to clarify, include a floor plan and/or site plan.

2.3.6.4 Observations. State the frequency and timing of observations.

2.3.6.5 Correlation. Indicate features affecting the correlation structure, such as longitudinal sequences of observations or clustering of units or subunits. Examples of clustering of units include litter relationships, grouping by housing unit, or grouping by enrollment cohort.

2.3.6.6 Blinding (masking). Wherever possible, make observations without knowing the status of the object of the observation. For example, in clinical studies, describe the method of blinding clinical observations so the observer does not know which treatment a group has received or the group to which a subject is assigned. Justify any unblinded observations.

2.3.6.7 Outcome Variables for Clinical Trials.

2.3.6.7.1 Outcome Definition. An outcome variable is a single observation on each subject. It is defined by specifying the event or observation and describing the way it is to be measured. For example, occurrence of event, time until event, duration of event, or magnitude of event are different outcomes for the same event. Include the units of measurement and any proposed data reduction methods, such as with a subject summary measure.

2.3.6.7.2 Primary Outcome. The primary outcome is the planned measure in the protocol that is the most important for evaluating the effect of the biological product. It is the outcome upon which the study conclusion is based. Most confirmatory efficacy studies should have one primary outcome to support each label claim. If substantively warranted, the primary outcome may be designed as a composite of more than one type of observation or a comparison between more than one summary measure. Specify the primary outcome in the protocol stage, and use it in the analysis stage.

2.3.6.7.3 Intermediate Measurements and Observations. Intermediate measurements or observations are sometimes used to determine whether an outcome is achieved. For example, body temperature may be a measurement that determines whether pyrexia was achieved.

2.3.6.8 Conclusion criterion. State the criteria for interpreting the results. For confirmatory studies, give the specific criterion for differentiating a satisfactory from an unsatisfactory conclusion. For efficacy studies, base the conclusion criteria on the size and relevance of the estimated effects. Do not base conclusions primarily on statistical measures which may accompany the estimate for the purpose of assessing its relative precision. For example, a 'p value' by itself is not a sufficient criterion.

2.3.6.9 Statistical methods.

2.3.6.9.1 State what is to be estimated. Often, the estimator will be a function comparing the responses of different groups in clinical trials.

2.3.6.9.2 State the method of calculating interval estimates, such as confidence intervals or credible sets, where applicable.

2.3.6.9.3 If hypothesis tests are planned, state the hypothesis. Use two-sided tests or justify the use of one-sided tests. As a general rule, set the significance (type 1 error) level of a one-sided test at half the significance level of a two-sided test to be consistent with confidence intervals.

2.3.6.9.4 Methods of statistical inference proceed from assumptions on which the underlying statistical model is based. Justify the assumptions by the nature of the response variable and study design.

2.3.6.9.5 Where a formal statistical model is appropriate, show the model in mathematical notation.

2.3.7 *Summary of changes.* Often a protocol is similar to a previously conducted study. Review of protocols is expedited by providing a summary of changes from a previously reviewed protocol, if applicable. Clearly identify the referenced protocol, preferably with the CVB Mail Log number. In some circumstances, a summary of changes may apply to similar protocols that are submitted concurrently.

3. Records.

3.1 *Purpose.* Records track the actual conduct of the study, noting important events and observations. Records support the quality of the data.

3.2 Recording Procedures.

3.2.1 Identify the applicable experimental protocol including the CVB Mail Log number(s).

3.2.2 Maintain legible and indelible records, per 9 CFR 116.1(a)(2). If electronic data capture systems are to be used, contact the CVB in advance to ensure acceptability.

3.2.3 Make records concurrently with each successive step in every study activity, per 9 CFR 116.1(a)(1).

3.2.4 Define abbreviations and acronyms.

3.2.5 Cross out errors with a single line so that the error remains legible. Clearly indicate the correction and why the correction was made. Have the person responsible for the correction initial and date it.

3.3 Information to Record.

3.3.1 Date and, if necessary, time.

3.3.2 Initials or signature of the person making the record.

3.3.3 Clinical or laboratory observations.

3.3.4 Identification and accountability of all product prepared, used, distributed, or returned.

3.3.5 Identification and accountability for all animals.

3.4 *Location of records.* Maintain all records generated in support of a license application on licensed premises, and have the records available for inspection at all times.

4. Data Analysis.

4.1 *Purpose.* Before the results of the study can be properly interpreted, they must be subjected to a thorough and objective analysis which evaluates the role of error in the study results. Two important types of error are random error (variance) and systematic error (bias). A proper statistical analysis includes an assessment of random error. A sensitivity analysis may shed light on bias.

4.2 *Statistical analysis.* With the final study report, submit a statistical package which includes the data and statistical analysis. The statistical analysis may include description, estimation, inference, or decision. The analysis should be consistent with the protocol. The proposed primary outcome (from the protocol) should be used. If the primary outcome changes from the protocol stage, clearly note and explain the change. For example, it may be necessary to alter the case definition of disease in the event significant mortality is observed, and mortality was not described as the primary outcome.

4.2.1 *Statistical methods.* Describe and justify any methods selected after examining the data or not specified in the protocol.

4.2.2 *Statistical summary.* Outline the analysis in enough detail so that another statistician could repeat it. Include the following, as appropriate:

4.2.2.1 *Data description.* Describe the data set. If the analysis was carried out on a subset of the data, clearly note this fact and include a justification.

4.2.2.2 Concise presentation of the data, such as graphical, tabular, and/or narrative summaries.

4.2.2.3 Assessment of the assumptions of the statistical model or methods.

4.2.2.4 Estimates of the specified effects and comparisons. Use interval estimates or accompany point estimates with a statistical measure of uncertainty due to randomness.

4.2.2.5 Inferences specified in the protocol.

4.2.2.6 Relevant features of the data that the analysis must take into account. Examples include animal housing arrangements that reflect clustering in an efficacy study or the timing of a sequence of laboratory tests.

4.2.2.7 Conclusions supported by the findings.

4.2.3 *Inferential approach.* Any of the major schools of statistical inference may offer a variety of legitimate approaches to data analysis. Ensure the assumptions, methods, and interpretation are consistent with the particular approach to inference taken by the statistical analysis. For example, a ‘p value’ should not be interpreted as a posterior probability. Ensure that the statistician reviews the final report. This is especially important when the conclusions based on the analysis are included in the final report, separate from the statistical analysis report.

4.3 *Sensitivity analysis.* When interpreting the results of a statistical analysis, consider the potential contribution of bias to inferences or estimates. Because bias can occur in subtle or unknown ways, and its effect is not measurable directly, it is important to evaluate the robustness of the conclusions expressed in the final report. For example, consider the sensitivity of the conclusions to various limitations of the data, potential deviations from the assumptions, and different approaches to data analysis or inference. A robust conclusion is one which would not be substantially affected under such alternatives.

5. Final Report

5.1 *Purpose.* Thoroughly describe the events and results of the study with the comprehensive objectivity expected of a scientific report. It should, by itself, be readily comprehensible to a reader familiar with scientific literature. Include references to relevant documents and information impacting the proper understanding of the study.

5.2 *Contents.* Address all topics included in the protocol. Describe what actually occurred in the study rather than state that the study was done according to the protocol. Point out and justify deviations from the protocol. Clearly denote changes in the primary outcome.

5.3 *Format.*

5.3.1 *Title.* State the title and report number.

5.3.2 *Summary.* Summarize the report.

5.3.3 *Introduction.*

5.3.3.1 *Background.* Include a summary of all similar studies previously initiated with the current, or related, products and a description of other relevant information.

5.3.3.2 *Objective.* If the report is meant to support the product’s intended use, include all proposed claims and indications.

5.3.4 References.

5.3.4.1 *Documents.* Refer to the study protocol, relevant 9 CFR Standard Requirements, Outlines of Production or other proprietary documents, and established scientific or regulatory guidelines.

5.3.4.2 *Glossary.* Define abbreviations, acronyms, trade names, or unusual terminology.

5.3.5 *Personnel.* Identify the report author, and list key study personnel.

5.3.6 *Sequence of events.* List or tabulate the sequence of important events. Give actual dates as well as the time relative to critical events, such as challenge.

5.3.7 *Materials.* State the composition of experimental products and other materials.

5.3.8 Methods.

5.3.8.1 Describe experimental or observational methods.

5.3.8.2 Note and justify protocol deviations.

5.3.8.3 Include a floor plan and/or site plan illustrating the housing of subjects in efficacy studies.

5.3.9 Results.

5.3.9.1 Summarize the observations recorded during the study.

5.3.9.2 Account for all subjects entering the study. Include subjects considered for enrollment but rejected on the basis of exclusion criteria.

5.3.9.3 Give the results of laboratory analyses including the laboratory conducting the testing.

5.3.9.4 Note other relevant findings whether or not related to the study objectives, such as adverse events observed in an efficacy trial.

5.3.10 *Data analysis.* Describe the major features of the statistical and sensitivity analyses.

5.3.11 *Discussion.* Discuss the clinical or substantive relevance of the results in the context of the product's development and other available data, including other studies initiated with the current or related products.

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5.3.12 *Conclusion*. State whether the data support the protocol's conclusion criterion. In confirmatory studies, state the label claim.

5.3.13 *Appendices and Attachments*

5.3.13.1 *Data*. Submit complete data in an electronic form amenable to analysis, as outlined on the CVB website:

Updated website 2018:
https://www.aphis.usda.gov/animal_health/vet_biologics/publications/16-CVBDataGuide.pdf

(~~http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth%2Fsa-vet_biologics%2Fet_vb_data_formats_overview~~). Submit data in its raw unaltered form, using the precision observed and without manipulation. Avoid entering the same data in more than one table whenever possible, and if not possible, clearly indicate where duplication has occurred.

5.3.13.2 *Software code*. Identify the software, and submit the programming code and computer output.

Other Reading.

Veterinary Services Memorandum No. 800.301 "Good Clinical Practice"

Abbreviations.

CVB	Center for Veterinary Biologics
PEL	Policy, Licensing, and Evaluation
VS	Veterinary Services, Animal and Plant Health Inspection Service, United States Department of Agriculture
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products