June 14, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.200

Subject: General Licensing Considerations: Study Practices and Documentation

To: Veterinary Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

These general licensing considerations provide 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 9 CFR 102.5 and 104.5.

II. REDESIGNATION

General Licensing Considerations for Efficacy Studies (formerly Veterinary Services Memorandum No. 800.200) has been redesignated as Veterinary Services Memorandum No. 800.202.

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-Licensing and Policy Development (CVB-LPD) 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 Center for Veterinary Biologics General Licensing Considerations, published as Veterinary Services Memorandums in the 800.200 series. Guidance may also be found in internationally harmonized guidelines generated through the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), published as Veterinary Services Memorandums in the 800.300 series.

IV. GUIDELINES

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

/s/ W. Ron DeHaven

W. Ron DeHaven
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Enclosure

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.* Each phase of the study should be completely documented. Documentation should be sufficient to capture the study's progress, and should at least include the following:

document	*phase*
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 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 (9CFR ' 101.2(1)). Consequently, such claims, indications, and cautions must be included in protocols and reports of confirmatory studies.

1.5 *Scientific standards*. Studies should be designed, conducted, analyzed and reported according to sound scientific principles. Accepted standards for objectivity and scientific rigor should be followed in all studies and reflected in documents associated with those studies.

1.6 *Statistical principles*. Statistical principles should be appropriately applied at all stages of development, from conceiving the initial research question, through 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 should state the objectives, describe the design, plan the execution and analysis, and specify the conclusion criteria.

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

2.3 *Content*. The protocol should include the following information.

2.3.1 *Objective.* Clearly state the explicit objective of the study. Differentiate between an exploratory and confirmatory study. For a confirmatory study, state the proposed label claim. The objective should be consistent with the type of study and its context in the product's development. It should be intended to answer the relevant research question. The objective of an exploratory study may be broadly stated and open ended, while the objective of a confirmatory study should be specific, explicitly stated, and aimed to support the proposed label statement.

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.

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 locations.

2.3.4 *Sequence of events.* State the proposed sequence of critical events.

2.3.5 *Materials*. Describe the formulations of the experimental products and other essential materials or reagents. For clinical trials, describe the nature of the placebo or active control treatment.

2.3.6 *Design considerations*. The study design should take into account the type of study and its objective as well as all relevant scientific features and pragmatic concerns. The study design should aim to reduce bias, increase precision, and estimate error. Some important considerations for doing so are:

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.

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

2.3.6.3 *Correlation*. Indicate features affecting the correlation structure, such as longitudinal sequences of observations or clustering of units or subunits.

2.3.6.4 *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.

2.3.6.5 *Blinding*. Describe the blinding methods or justify unblinded observations.

2.3.6.6 *Outcome.* State the primary outcome.

2.3.6.7 *Estimator*. State the quantity to be estimated, which is often a function relating two variables, such as their difference.

2.3.7 *Unit selection*. Describe the selection of the experimental units and criteria for inclusion or exclusion.

2.3.7.1 For observational studies give the sampling frame and sampling method.

2.3.7.2 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.

2.3.8 *Observations*

2.3.8.1 *Observation times*. State the frequency and time of observations.

2.3.8.2 *Blinding (masking)*. Wherever possible, observations should be made 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 knows neither which treatment a group has received nor the group to which a subject is assigned.

2.3.9 *Outcome variables*. State the outcomes to be measured. For confirmatory studies, specify which is the primary outcome.

2.3.9.1 *Outcome definition*. An outcome 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. Include the units of measurement and any proposed data reduction methods, such as by subject summary measures.

2.3.9.2 *Primary outcome.* Since the conclusion of a confirmatory study will be based on the primary outcome, it should be the outcome providing the most relevant evidence supporting the study's objective. Specify a single primary outcome for each 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.

2.3.10 *Conclusion criterion*. State the criteria for interpreting the results. For confirmatory studies, give the specific criterion for differentiating a satisfactory from an unsatisfactory conclusion. Conclusion criteria should be based 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, although it may be considered necessary in order to accept the precision of the particular estimate which forms the conclusion criterion.

2.3.11 *Statistical methods*.

2.3.11.1 Identify the statistician responsible for overseeing the appropriate application of statistical principles at all stages of study development. The responsible statistician should be experienced in the application of statistical theory to scientific research and familiar with the logistics and scientific basis of the study.

2.3.11.2 State what is to be estimated. Often, the estimator will be a function comparing the responses of different groups.

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

2.3.11.4 If hypothesis tests are planned, state the hypothesis. Use two-sided tests or justify the use of one-sided tests. The significance (type 1 error) level of a one-sided test should generally be set at half the significance level of a two-sided test to be consistent with confidence intervals and avoid bias.

2.3.11.5 Methods of statistical inference proceed from assumptions on which the underlying statistical model is based. The assumptions should be justified by the nature of the response variable and study design.

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

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.

3.2.2 Maintain legible and indelible records

3.2.3 Make records concurrently with each successive step in every study activity.

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. The person responsible for the correction should 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 of 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.

4.2.1 *Data.* Submit the complete data in a form amenable to analysis, as outlined in VS Memorandum 800.96.

4.2.2 *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.

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

4.2.4 *Statistical methods*. Methods selected after examining the data or not specified in the protocol should be described and justified.

4.2.5 *Statistical summary*. Outline the analysis in enough detail so that another statistician could repeat it. Include one or more of the following, where appropriate.

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

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

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

4.2.5.4 Inferences specified in the protocol.

4.2.5.5 Relevant features of the data.

4.2.5.6 Conclusions supported by the findings.

4.2.6 *Inferential approach*. Any of the major schools of statistical inference may offer a variety of legitimate approaches to data analysis. The assumptions, methods, and interpretation should all be 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. Towards that end, the statistician should also review the final 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. Report.

5.1 *Purpose*. The final report should 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. The report should include references to relevant documents and information impacting the proper understanding of the study.

5.2 *Contents.* The report should address all topics included in the protocol. It should describe what actually occurred in the study rather than state that the study was done according to the protocol. Deviations from the protocol should be pointed out and justified.

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 9CFR 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's 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.

5.3.9 *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.

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.

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*.

Appendix

References.

VS Memorandum 800.96	Electronic Data Files for Statistical Analysis
VS Memorandum 800.301	Good Clinical Practice

Abbreviations.

CVB	Center for Veterinary Biologics
GLC	General Licensing Considerations
LPD	Licensing and Policy Development
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