104

Guidance for Industry

Content and Format of Effectiveness and Target Animal Safety Technical Sections and Final Study Reports For Submission to the Division of Therapeutic Drugs for Non-Food Animals

This guidance supercedes the guidance of September 1999. (This document was revised to include the disclaimer in the paragraph below and to update the address to submit

Guidance #85 entitled "Good Clinical Practices" became final on May 15, 2001. Until the Center revises guidance #104, sponsors should follow the recommendations in guidance #85 when differences among the guidances occur. If you have any questions, please contact Herman Schoenemann (HFV-120), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (301) 827-0220, e-mail: hschoene@cvm.fda.gov.

This document is intended to provide guidance on the content and format of technical section submissions for effectiveness and target animal safety and final study reports in support of these technical sections. This guidance represents the Food and Drug Administration's (FDA's) current thinking on the content and format of effectiveness and safety technical sections and final study reports for submission solely to the Division of Therapeutic Drugs for Non-Food Animals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

Comments and suggestions regarding this document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

For questions regarding this guidance document, contact Tania D. Woerner, Center for Veterinary Medicine (HFV-114), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (301) 827-0129, e-mail: twoerner@cvm.fda.gov .

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Veterinary Medicine (CVM)
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Table of Contents

I. Foreword

This guidance document was prepared to enable sponsors to submit "quality" data submissions, which will allow for a more efficient review by CVM. The scope of this document is limited to submissions to the Division of Therapeutic Drugs for Non-Food Animals (HFV-110).

A complete New Animal Drug Application (NADA) must be composed of all the sections identified in 21 CFR §514.1 and as stated on the Form FDA 356V. In order to facilitate the approval of NADAs, CVM now accepts major data submissions for individual sections of an NADA (technical sections) under the Investigational New Animal Drug (INAD) file. To the extent possible, CVM reviews each technical section independently. When CVM finds that all the sections are complete the sponsor may file an "administrative NADA". This guidance document will focus exclusively on the effectiveness and the target animal safety technical sections reviewed by the Division of Therapeutic Drugs for Non-Food Animals.

In CVM's efforts to find ways of improving its efficiency, it was discovered that reviewers often found it difficult to locate specific elements within a technical section and determine if all necessary elements of the technical section were present in the submission. This document addresses that problem and is intended to provide guidance on the suggested content and format of technical section submissions. Adherence to this guidance should assist CVM reviewers in locating and reviewing this information. The information contained in this guidance applies whether effectiveness and target animal safety data are submitted as individual technical sections under an INAD or collectively as part of a complete NADA. This document also provides guidance on the content and format of a final study report, which is a fundamental component of these technical sections.

Other relevant documents (where appropriate, Office of Management and Budget (OMB) information control numbers are in parentheses following the title of the document) include: 21 CFR Part 511 – New Animal Drugs for Investigational Use (OMB 0910-0017), 21 CFR Part 514 – New Animal Drug Applications (OMB 0910-0037), 21 CFR Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs) (OMB 0910-0119), 21 CFR Part 11 – Electronic Records; Electronic Signatures (OMB 0910-0303), Good Target Animal Study Practices: Clinical Investigators and Monitors (May 1997), Target Animal Safety Guidelines for New Animal Drugs (June 1989), Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials (November 1994), and CVM's Policy and Procedures Manual 1240.3040. References in this guidance to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

These documents, or references to them, can be found on CVM's website at **http://www.fda.gov/cvm**. Paper copies can be obtained from the Communications Staff (HFV-12), Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

II. Glossary

Administrative New Animal Drug Application: The NADA submission that is filed for the purpose of seeking approval of the new animal drug for the tested claims after CVM has issued technical section complete letters for all technical sections.

Adverse Drug Experience (ADE): Any adverse event associated with the use of an investigational or approved new animal drug, whether or not considered to be drug related.

Animal Drug Availability Act of 1996 (ADAA): Legislation enacted October 9, 1996, to amend the Federal Food Drug and Cosmetic Act. The purpose of the ADAA is to facilitate the approval and marketing of new animal drugs and medicated feeds. Among other items, the ADAA revised the definition of substantial evidence, which is the standard for demonstrating effectiveness.

Clinical Study: A single scientific experiment conducted to test at least one scientific hypothesis relevant to the proposed claim(s) made for a new animal drug.

Dosage: Dosage includes the dose or dose range, dosing frequency and dosing duration.

Experimental Phase Completion Date (for clinical studies): The date on which collection of all raw data is complete.

Experimental Phase Initiation Date (for clinical studies): The date on which animals are first identified with a treatment.

Final Study Report: The comprehensive description of the study written after its conclusion. This report includes a description of the objective(s), experimental materials and methods, and a presentation and critical scientific evaluation of the results (including statistical analyses where appropriate).

Good Laboratory Practices (GLPs): The regulations governing the conduct of nonclinical laboratory studies (21 CFR Part 58).

Investigator: An individual qualified by training and experience that is entrusted with the implementation of the study protocol, collecting study data, and the overall conduct of the clinical study.

Monitor: An individual qualified by training and experience who represents the sponsor in overseeing the investigator's implementation of a protocol and progress of the clinical study and determines whether the clinical study is conducted in accordance with all applicable requirements.

Nonclinical Laboratory Study: *In vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. See §58.3 (d) for a more detailed definition.

Protocol: A document signed and dated by the investigator for clinical studies (or study director for GLP studies) and the sponsor, that states the rationale and objectives of the study and all methods and conditions under which the study is to be performed and managed. The term protocol includes all protocol amendments.

Protocol Amendment: A change or modification of the protocol, effected prior to the implementation of the protocol or the execution of the changed or modified task, that is signed and dated by the investigator (or study director) and sponsor and incorporated into the protocol.

Protocol Deviation: A departure from the procedures delineated in the protocol, after the protocol has been signed by the investigator (or study director) and sponsor.

Raw Data (for clinical studies): Any worksheets, calibration data, records, memoranda and notes of original observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, computer printouts, magnetic, electronic or optical media, information recorded from automated instruments, and hand recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

Raw Data (for GLP studies): See §58.3 (k) for a complete definition.

Report Amendment: Any addition, deletion or correction to the final study report. A report amendment clearly identifies that part of the study report that is being added, deleted or corrected and the reasons for the addition, deletion, or correction, and is signed and dated by the authors.

Study Director: The individual responsible for the overall conduct of a nonclinical laboratory study.

Study Documentation: All records in any form (including documents, magnetic and optical records) describing methods and conduct of the study, factors affecting the study, and any actions taken. These records include, but are not limited to: protocol, raw data, reports, standard operating procedures (SOPs), reference materials, and specimens.

Study Initiation Date: The date the study protocol is signed by the investigator for clinical studies or is signed by the study director for GLP studies.

Study Completion Date: The date the final study report is signed by all authors for clinical studies or is signed by the study director for GLP studies.

Substantial Evidence: Evidence consisting of one or more adequate and well-controlled studies, such as, a study in a target species, a study in laboratory animals, a field investigation, a bioequivalence study, or an *in vitro* study, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Technical Section: An organizational element of an NADA as defined in §514.1 and outlined in the Form FDA 356V. Each technical section must support a condition of approval required by CVM. All studies supporting a single technical section should be submitted as well as other relevant information such as referenced literature, foreign market experience, etc. A technical section should also contain information on the proposed conditions of use and/or labeling, and the relevant portion(s) of the FOI Summary.

III. Effectiveness

A. Content and format of the technical section

1. Cover letter

The content of the cover letter is administratively used to route the submission to the proper review personnel. Therefore, it is essential to make the purpose of the submission explicit in this letter. The following elements should be included in the cover letter:

- INAD file number
- Name, address, and telephone number of the sponsor
- Drug name (include trade name and generic name)
- Specific purpose of the submission
- Proposed indications

The cover letter and supporting information should be mailed to: Center for Veterinary Medicine, Document Control Unit, HFV-199, 7500 Standish Place, Rockville MD 20855.

2. Table of contents

A general table of contents for the technical section is recommended. Within a particular final study report or volume, a more detailed table of contents is also recommended.

3. Dosage justification and dose-response characterization

Following the enactment of the ADAA, dosage justification and characterization of critical aspects of the dose-response relationship are no longer necessarily part of the determination of effectiveness by substantial evidence. Dosage justification and dose-response characterization may be supported by several means, including but not limited to, dose titration studies, pilot studies or literature (as opposed to dose confirmation). Confirmation of the effectiveness of the selected dose or dose range continues to require demonstration by substantial evidence. If a dose range is selected, characterization of the dose-response relationship over the dose range selected will generally be needed. A summary of the information used for the justification of dosage and characterization of dose-response relationship should be submitted. Copies of literature and other studies should be included.

4. Summary of studies providing substantial evidence of effectiveness

There are a variety of adequate and well-controlled studies (as defined by §514.117) that may be used to support the effectiveness of the new animal drug. The overall summary of effectiveness data should generally cover the developmental history of the technical section and summaries of all adequate and well-controlled studies. The developmental history is a timeline that describes agreements and discussions between the sponsor and CVM and regulatory decisions made by CVM. A summary of the adequate and well-controlled studies should include the following information (at a minimum):

- Number and identification of adequate and well-controlled effectiveness studies
- Type of studies (clinical field, pharmacokinetic, *in vitro*, etc.)
- Study Initiation Date, Experimental Phase Initiation/Completion Dates, Study Completion Date
- Number of investigational (treated and control) animals per study
- Formulation of drug used in each study (e.g., final market formulation, batch number, and other pertinent descriptors)
- Brief description of results for each study

A tabular format is suggested as an efficient way to summarize major aspects of studies. For example:

Study no.	**Study type: Effectiveness**	**Study Initiation & Completion Dates**	**Exper. Phase Initiation & Completion Dates**	**No. of Animals**	**Drug Formulation**
C030-541-98	Clinical field	3/10/95 - 6/10/95	4/11/95-5/11/95	240 adult horses; 120 treated, 120 control	final market formulation
C028-551-98	Pharmaco-kinetic	1/12/95-4/15/95	2/13/95-3/13/95	20 adult ponies	batch #404

More detailed tables may be used to describe effectiveness results. Although tables are preferable, text summaries are also acceptable. An overall summary of product effectiveness should also appear in this section.

5. Final study reports of studies providing substantial evidence of effectiveness

The content and format of a final study report is described later in this document. Each study providing substantial evidence of effectiveness should be individually summarized in a final study report format with associated appendices.

6. All information, other than substantial evidence, pertinent to effectiveness.

This section should contain any other information that may be pertinent to evaluating effectiveness of the product. Under §514.1(b)(8)(iv), CVM may refuse an application if it does not contain all information pertinent to the evaluation of the safety and effectiveness of the new animal drug and related new animal drugs. Information such as reports in the scientific literature, other studies conducted with the product outside the U.S., or any evaluations made by the sponsor's veterinary consultants or staff should be included. Summaries of this information are acceptable.

7. Foreign market experience

This section includes any adverse drug events (ADEs) or items such as a report on the approximate number of units of the product sold outside of the U.S. Inclusion of the foreign approved product package insert (with English translation) is recommended.

8. Product labeling

Draft product labeling should be submitted at the time the technical section is submitted. Emphasis should be placed on sections of product labeling which relate to product effectiveness, e.g., indications, dosage and administration, clinical effectiveness, cautions, and warnings. Submission of product labeling on an appropriate electronic medium is recommended.

9. FOI summary

All sections of the FOI (Freedom of Information) summary that pertain to product effectiveness should be submitted with the technical section. Submission of the FOI summary information on an appropriate electronic medium is recommended.

B. Content and format of an effectiveness final study report

One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective. The required characteristics of an adequate and well-controlled study are described in §514.117(b). The preparation of a final study report (FSR) is a required component of an adequate and well-controlled study. The FSR should be a comprehensive, stand-alone document that provides a clear explanation of the study objective(s), experimental materials and methods and a presentation and critical scientific evaluation of the results. The FSR should be written when collection of all raw data is complete. The effectiveness technical section should contain FSRs for each adequate and well-controlled study and reports/abstracts of corroborating studies conducted in support of a determination of effectiveness.

A study is not considered complete until a FSR is signed by the authors (all individuals involved in the preparation of the FSR). The authors should sign and date and include in the FSR a brief statement of their contributions to the FSR. Any corrections or additions to the FSR should be in the form of an amendment by the authors. The amendment should clearly identify that part of the FSR that is being added or corrected and the reason for the correction or addition, and should be signed and dated by the authors.

The FSR should contain the following elements:

1. Title page

The title page should contain the following information:

- Title of protocol/study
- Protocol version and study number (this should also appear on each page of the report)
- Investigational new animal drug generic and trade name
- Proposed indication(s)
- Sponsor name and address
- Investigator(s) name and address
- Study site(s) name and address
- Study initiation and completion dates
- Experimental initiation and completion dates
- Signature of report author(s), date signed, title of author(s)

2. Table of contents

The table of contents should be comprehensive, identifying each section and subsection (and associated page number) of the report. The insertion of tabs is recommended for the principal sections.

3. Summary

A brief summary of the materials and methods and results of the study should be provided. It should describe the critical features of the study, e.g., target population, primary parameters, and adverse reactions, and any guidance or regulations that were followed during the conduct. The summary may include text, tables, and graphs.

4. Objective(s)

A statement under this heading should describe the overall objective(s) of the study as stated in the study protocol.

5. Study schedule

A chronological representation of key events of the study and the dates on which they occurred, including the study initiation and completion dates and the experimental initiation and completion dates.

6. Study design

The rationale and description of the chosen experimental design of the study should be provided. The number of animals per treatment and a description of each treatment should be included. The nature of the control group should be discussed. The experimental unit should be defined. An explanation of how the animals were housed should be provided. The randomization procedures, variables used, e.g., weight, gender, and age, and statistical programs for randomization should be described completely. The practical arrangements to be followed to allocate animals to treatment groups and treatment groups to experimental units should be discussed. If blinding was appropriate to the study design, detail the extent of blinding, how the blinding was accomplished, and the circumstances under which the treatment code may be revealed.

7. Study procedures

This section should include all details necessary to reconstruct and understand the experimental materials and methods used to conduct the study. Deviations from the protocol should be discussed.

7.1 Investigational new animal drug and control

7.1.1 Description

The description of the investigational new animal drug and control should permit an unambiguous determination of the specific formulation. Characteristics such as lot or batch number, trade name, formulation, dosage form, or manufacturing site may prove useful.

7.1.2 Storage conditions

The storage conditions of the investigational new animal drug and control during the conduct of the study should be described.

7.1.3 Material Safety Data Sheet (MSDS)

The MSDS may be attached as an appendix to this report.

7.2 Investigational animals

7.2.1 Description

A complete description of the investigational (control and treated) animals should be included. This description should include, where appropriate, the number of treated and control animals, species/breed, age, gender, body weight range, source of supply, and procedures used for identification, e.g., neckband and tattoo. The physiological status, e.g., lactating, pregnant, or prepubertal, of the animals should also be described.

7.2.2 Owner Consent Forms

The owner consent forms should be attached as an appendix to this report.

7.2.3 Inclusion/exclusion criteria

The objective selection criteria used to admit animals to the study should be described, including any diagnostic requirements, e.g., physical examination, body temperature, or reproductive status. The rationale for and description of the inclusion and exclusion criteria (which prevent an animal from entering the study) should be included. If any animal is used in the study that failed to meet the inclusion criteria, the reason should be provided.

7.2.4 Acclimation of investigational animals

An acclimation period allows animals to adapt to the study environment, e.g., housing, handling, and feeding practices. The final study report should describe the location of the animals during the acclimation period, the length of the acclimation period, any medication(s) and/or vaccines administered during this period, and any baseline data collected prior to dose administration.

7.3 Analytical methods

For each analytical method used in the conduct of this study, include, at a minimum, a description of the method, a brief methodology (including sample collection, preparation and storage; validation; quality control procedures; and supportive relevant scientific references), and objective criteria and procedures to assess the analytical results. A certification that all method validations were performed before the initiation of the study should be included. If validations were not performed before the start of the study a statement describing the mitigating reasons should be included.

7.4 Study facilities

7.4.1 Identification and description

The name, address, and complete description of the study facilities should be provided. Such a description could include a general description of the housing unit(s) including

dimensions of the pertinent areas used during any phase of the study. Diagrams may prove useful to convey this information.

7.4.2 Management procedures

General management procedures, e.g., equipment maintenance and environmental control (temperature, humidity, airflow), may have bearing on the study outcome and welfare of the animals and should be described. Where appropriate, the type, frequency and duration of exercise provided to the animals should be described.

7.5 Feed and Water

7.5.1 Diets

The diets fed to the investigational animals should meet the nutritional requirements of the animals. When necessary, a qualitative and quantitative description of the dietary ingredients should be provided. The frequency of feedings and the quantities of feed offered and refused should be described. When the test article is administered in feed, drug feed assays should be discussed, especially in terms of proper drug administration. Discuss differences, if any, in the dietary feed intake between the treated and control animals.

7.5.2 Water

The quality and availability of water offered to the animals and water delivery systems should be described.

7.6 Treatment administration

A justification for and description of the selected dosage, dosage regimen, route of administration, and duration should be included. Any problems encountered with dosing should be discussed as well as observations regarding palatability (if applicable).

7.7 Concomitant medications/therapies

The type, quantity and duration of concomitant medications/therapies should be discussed in this section. The rationale for use and impact of the medications/therapies on the study outcome, e.g., drug interaction or effect on a study parameter, should be discussed.

7.8 Criteria for animal removal from a study

It is sometimes necessary to remove an animal from study due to sickness, injury or other reasons. The specific criteria for removal should be detailed as well as the procedure for removal and, if appropriate, replacement.

7.9 Necropsy procedures

Details of the gross necropsy performed on dead or moribund animals to determine cause of death should be included.

7.10 Animal and drug accountability and disposition

The final disposition of all investigational animals and the investigational new animal drug and control article should be described.

8. Study variables/observations

8.1 Variables measured for evaluating study objectives

Observations include any inspection or examination of investigational animals. The rationale for the variables selected to test the objective of the study should be discussed in detail. In addition, the methods used in assessing the variable should be explained or referenced. The frequency of assessment and the criteria used to characterize the measurement of the variable should be stated. If measurement of a variable is derived, the calculations used in the derivation should be provided.

For example, in the evaluation of an anti-inflammatory drug for horses, lameness is graded on a scale of 1-5. The definition of each of the grades should be provided and the scale referenced. In addition, a reason why lameness is an acceptable variable to test effectiveness of an anti-inflammatory drug should be provided. The frequency of lameness assessment should be stated and the procedure used to grade the lameness discussed.

8.2 Other observations recorded during the study

All other types of observations should be discussed such as animal care observations, food consumption observations, etc.

9. Data calculations and statistical methodologies and analyses

A description of all transformations, calculations, or operations performed on the data and the statistical methods employed for analyzing the data should be included. The statistical portion of the report is not a printout of the data analysis (which should be included as an appendix) but rather, is a description of the data and procedures. Identify the differences that exist, if any, between the data set subjected to statistical analyses and the complete raw data. Define the experimental unit and the number of replicates per treatment. The statistical methodology should be described including the hypotheses tested, any estimated parameters or assumptions and any specific statistical model used. If any data transformations were performed, a rationale for the choice of transformation as well as the impact on treatment effects should be discussed. Define how the results were used to draw conclusions about the study's objective(s) and the appropriateness of the choice of statistical method. Where the actual transformations, calculations, or operations performed on the data or the actual statistical methods employed to analyze the data differ from that stated in the protocol, a rationale for such deviation should be included.

10. Results

All data collected during the study should be summarized and analyzed. A description of how the results for each protocol-defined parameter support effectiveness should be included. Results should be presented as text, tables or graphs. The exact location (appendix page numbers) of the supporting raw data should be referenced. Tables and graphs should be concise and user-friendly, since individual data will be located in the appendices.

11. Conclusions/discussion

An overall statement of the conclusions drawn from the analysis of the data should be included. The assessment of effectiveness should compare and contrast the effects that were to be achieved and the clinical endpoints that were to be reached before effectiveness could be claimed with the actual study observations. Furthermore, a description of all circumstances that

may have affected the quality or integrity of the data should be included. New or unexpected findings and their impact on the study outcome should be identified. Adverse events and their potential impact and any results, which may be inconsistent with the overall study conclusions, should also be discussed in detail.

12. Personnel

The name of the investigator and other personnel involved in the study should be included.

13. Reports

The signed and dated reports of each scientist or other professional, e.g., pathologists and statisticians, involved in the study should be included. Reports may be included in the appendices.

14. Accuracy and Completeness Statement

A statement, signed and dated by the investigator, attesting to the accuracy and completeness of the FSR and stating whether the data were collected in compliance with the study protocol, applicable guidance documents, and regulatory requirements should be included.

15. Location of specimens, raw data, and the final study report

The location where all study documentation is to be stored should be included.

16. Appendices

All study documentation should appear in the appendices of the FSR. For a definition of study documentation, see the glossary of this guidance.

IV. Target Animal Safety

A. Content and format of the technical section

1. Cover letter

The content of the cover letter is administratively used to route the submission to the proper review personnel. Therefore, it is essential to make the purpose of the submission explicit in this letter. The following elements should be included in the cover letter:

- INAD file number
- Name, address, and telephone number of the sponsor
- Drug name (include trade name and generic name)
- Specific purpose of the submission
- Proposed indications

The cover letter and supporting information should be mailed to: Center for Veterinary Medicine, Document Control Unit, HFV-199, 7500 Standish Place, Rockville MD 20855

2. Table of contents

A general table of contents for the technical section is recommended. Within a particular final study report or volume, a more detailed table of contents is also recommended.

3. Summary of target animal safety studies

The overall summary of target animal safety should cover the developmental history of the technical section and summaries of safety study results. The developmental history is a timeline that describes agreements and discussions between the sponsor and CVM, and regulatory decisions made by CVM. The safety summary should include the following information (at a minimum):

- Number and identification of target animal safety studies
- Type of studies (toxicity, tolerance, reproductive safety, etc.)
- Study Initiation Date, Experimental Phase Initiation/Completion Dates, Study Completion Dates
- Number of investigational animals (treated and control) per study

- Formulation of drug used in each study (e.g., final market formulation, batch number, and other pertinent descriptors)
- Brief description of results for each study

A tabular format is suggested as an efficient way to summarize major aspects of studies. For example:

Study no.	**Study type: Safety**	**Study Initiation & Completion Dates**	**Exper. Phase Initiation & Completion Dates**	**Number of animals**	**Drug Formulation**
C032-542-97	Toxicity (0,1,3,5X)	3/10/95 - 6/10/95	4/11/95-5/11/95	40 adult ponies; 10 per treatment group	final market formulation
C021-552-97	Tolerance	1/12/95-4/15/95	2/13/95-3/13/95	10 adult ponies	final market formulation

More detailed tables may be used to elaborate upon specific target animal safety study results. Although tables are preferable, text summaries are also acceptable.

4. Final study reports of target animal safety studies

Non-clinical laboratory safety studies must be conducted in compliance with 21 CFR Part 58. If any of the safety studies are not conducted in compliance with 21 CFR Part 58, a brief statement as to the reason for noncompliance and why the deviations do not invalidate the study shall be included as required by §514.111(a)(11).

Each safety study submitted in support of approval must be summarized in a final study report consistent with §58.185. This guidance also provides a suggested format. Target animal safety studies typically include toxicity, tolerance, and reproductive safety studies.
See CVM's Target Animal Safety Guideline for New Animal Drugs (June 1989) for additional information on these safety studies.

5. All other information pertinent to target animal safety

This section should contain any other information that may be pertinent to evaluating product safety. Consistent with §514.1(b)(8)(iv), CVM may refuse an application if it does not contain all information pertinent to the evaluation of the target animal safety and effectiveness of the new

animal drug and related new animal drugs. Information such as reports in the scientific literature, other studies conducted with the product outside the U.S. or any evaluations made by the sponsor's veterinary consultants or staff should be submitted. Summaries of this information are acceptable.

6. Foreign market experience

This section includes, among other items, the approximate number of units of the product sold outside of the United States as well as any adverse reaction reports. Inclusion of the foreign approved product package insert (with English translation) is recommended.

7. Product labeling

Draft product labeling should be submitted at the time the technical section is submitted. Emphasis should be placed on sections of product labeling that relate to target animal safety, e.g., contraindications, precautions, and toxicity. Submission of product labeling on an appropriate electronic medium is recommended.

8. FOI summary

The section of the FOI (Freedom of Information) summary that relates to target animal safety should be submitted at the time the technical section is submitted. Submission of the FOI summary information on an appropriate electronic medium is recommended.

B. Content and format of a final study report for a safety study

A nonclinical laboratory study, e.g., a target animal safety study, must be conducted in compliance with the Good Laboratory Practices regulations (21 CFR Part 58). One aspect of that compliance is the preparation of a final study report (FSR). An FSR must be prepared for each nonclinical laboratory study and must include the information required in §58.185. The FSR should be a comprehensive, stand-alone document that provides a clear explanation of the study objective(s), experimental materials and methods and a presentation and critical scientific evaluation of the results. The FSR should be written when collection of all raw data is complete. The target animal safety technical section should contain FSRs for each study conducted in support of target animal safety.

The FSR shall be signed and dated by the study director (§58.185(b)). Any corrections or additions to the FSR shall be in the form of an amendment by the study director. The amendment

shall clearly identify that part of the FSR that is being added or corrected and the reason of the correction or addition, and shall be signed and dated by the person responsible (§58.185(c)).

The FSR should contain the following elements:

1. Title page

The title page should contain the following information:

- Title of protocol/study
- Protocol version and study number (this should also appear on each page of the report)
- Investigational new animal drug generic and trade name
- Proposed indication(s)
- Sponsor name and address
- Testing facility name and address
- Study director name and address
- Quality assurance name and address
- Study initiation and completion dates
- Experimental initiation and completion dates
- Study director signature and date
- Report author(s) signature and date

2. Table of contents

The table of contents should be comprehensive, identifying each section and subsection (and associated page number) of the report. The insertion of tabs is recommended for the principal sections.

3. Summary

A brief summary of the materials and methods, and results of the study should be provided. It should describe the critical features of the study, e.g., target population, primary parameters, and adverse reactions, and any guidance or regulations that were followed during the conduct. The summary may include text, tables, and graphs.

4. Objective(s)

A statement under this heading shall describe the overall objective(s) of the study as stated in the study protocol (§58.185(a)(2)).

5. Study schedule

A chronological representation of key events of the study and the dates on which they occurred, including the study initiation and completion dates and the experimental initiation and completion dates.

6. Study design

6.1 Description of treatment groups/experimental design

A rationale and description of the chosen experimental design, e.g., cross-over or Latin square, should be provided. The number of animals per treatment group and a description of each treatment group are needed. The nature of the control group should also be discussed The experimental unit should be defined. An explanation of how the animals were housed should be provided.

6.2 Method of assignment to treatment group

A complete description of the procedure and type (randomization or stratification) of the assignment method should be provided. A discussion of the total number of animals and the variables used for randomization, e.g., weight, gender, and age, should be included.

6.3 Blinding

If blinding is appropriate to study design, detail the extent of blinding, how the blinding was accomplished, and the circumstances under which the treatment code may be revealed.

7. Study procedures

The final study report must include the procedures stated in the protocol (§58.185(a)(2)) and describe all methods used (§58.185(a)(6)). This section should include all details necessary to

reconstruct and understand the experimental materials and methods used to conduct the study. Deviations from the protocol should be discussed.

7.1 Test and control articles

7.1.1 Description

A description of the test (investigational new animal drug) and control article(s) must be identified in the report by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics (§58.185(a)(4)). Other identifying characteristics may include lot or batch number, trade name, formulation, dosage form, or manufacturing site.

7.1.2 Storage conditions

The storage conditions of the test and control articles during the conduct of the study should be described.

7.1.3 Stability

The stability of the test and control articles under the conditions of administration must be described (§58.185(a)(5)).

7.1.4 Material Safety Data Sheet (MSDS)

The MSDS may be attached as an appendix to this report.

7.2 Investigational animals

7.2.1 Description

A complete description of the investigational (control and treated) animals shall be included (§58.185(a)(7)). This description must include, where appropriate, the number of treated and control animals, species/breed, age, gender, body weight range, source of supply, and procedures used for identification, e.g., neckband and tattoo.

The physiological status, e.g., lactating, pregnant, or prepubertal, of the animals should also be described.

7.2.2 Owner Consent Forms

The owner consent forms (if appropriate) should be attached as an appendix to this report.

7.2.3 Inclusion/exclusion criteria

The selection criteria used to admit animals to the study should be described, including any diagnostic requirements, e.g., physical examination, body temperature, or reproductive status. The rationale for and description of the inclusion and exclusion criteria should be included. If any animal is used in the study that failed to meet the inclusion criteria, the reason should be provided.

7.2.4 Acclimation of investigational animals

An acclimation period allows animals to adapt to the study environment, e.g., housing, handling, and feeding practices. The final study report should describe the location of the animals during the acclimation period, the length of the acclimation period, any medication(s) and/or vaccines administered during this period, and any baseline data collected prior to dose administration.

7.3 Analytical methods

For each analytical method used in the conduct of this study, include, at a minimum, a description of the method, a brief methodology (including sample collection, preparation and storage; validation; quality control procedures; and supportive relevant scientific references), and objective criteria and procedures to assess the analytical results. A certification that all method validations were performed before the initiation of the study should be included. If validations were not performed before the start of the study a statement describing the mitigating reasons should be included.

7.4 Study facilities

7.4.1 Identification and description

The name and address of the study facilities must be provided (§58.185(a)(1)). A complete description of these facilities should be provided. Such a description could include a general description of the housing unit(s) including dimensions of the pertinent areas used during any phase of the study. Diagrams may prove useful to convey this information.

7.4.2 Management procedures

General management procedures, e.g., equipment maintenance and environmental control (temperature, humidity, airflow), may have bearing on the study outcome and welfare of the animals and should be described. Where appropriate, the type, frequency and duration of exercise provided to the animals should be described.

7.5. Feed and Water

7.5.1 Diets

The diets fed to the investigational animals should meet the nutritional requirements of the animals. When necessary, a qualitative and quantitative description of the dietary ingredients should be provided. The frequency of feedings and the quantities of feed offered and refused should be described. When the test article is administered in feed, drug feed assays should be discussed, especially in terms of proper drug administration. Discuss differences, if any, in the dietary feed intake between the treated and control animals.

7.5.2 Water

The quality and availability of water offered to the animals and water delivery systems should be described.

7.6 Treatment administration

A description of the dosage, dosage regimen, route of administration, and duration shall be included (§58.185(a)(8)). Any problems encountered with dosing should be discussed as well as observations regarding palatability (if applicable).

7.7 Concomitant medications/therapies

The type, quantity and duration of concomitant medications/therapies should be discussed in this section. The rationale for use and impact of the medications/therapies on the study outcome (e.g., drug interaction or effect on a study parameter) should be discussed.

7.8 Criteria for animal removal from a study

It is sometimes necessary to remove an animal from study due to sickness, injury or other reasons. The specific criteria for removal should be detailed as well as the procedure for removal and, if appropriate, replacement.

7.9 Necropsy procedures

Details of gross necropsy and histopathology should be included. The number of animals, measurements obtained, e.g., clinical pathology parameters, and tissues examined and saved should be listed.

7.10 Animal and drug accountability and disposition

The final disposition of all investigational animals (number and procedure for disposal) and the investigational new animal drug and control article should also be described.

8. Study variables/observations

8.1 Variables measured for evaluating study objectives

Observations include any inspection or examination of investigational animals. The rationale for the variables selected to test the objective of the study should be discussed in detail. In addition, the methods used in assessing the variable should be explained or referenced. The frequency of assessment and the criteria used to characterize the measurement of the

variable should be stated. If measurement of a variable is derived, the calculations used in the derivation should be provided.

For example, in a safety study for an injectable product to be administered intramuscularly, injection site observations should record the presence and degree of heat, swelling, redness and pain. These variables can be scored and used objectively to describe adverse effects associated with administration of the drug and/or the placebo.

8.2 Other observations recorded during the study

All other types of observations should be discussed such as animal care observations, food consumption observations, etc.

9. Data calculations and statistical methodologies and analyses

A description of all transformations, calculations, or operations performed on the data (§58.185(a)(11)) and the statistical methods employed for analyzing the data (§58.185(a)(3)) must be included. The statistical portion of the report is not a printout of the data analysis (which should be included as an appendix) but rather, is a description of the data and procedures. The differences that exist, if any, between the data set subjected to statistical analyses and the complete raw data should be identified. The experimental unit and the number of replicates per treatment should be defined. The statistical methodology should be described including the hypotheses tested, any estimated parameters or assumptions and any specific statistical model used. If any data transformations were performed, a rationale for the choice of transformation as well as the impact on treatment effects should be discussed. A description of how the results were used to draw conclusions about the study's objective(s) and the appropriateness of the choice of statistical method should be provided. Where the actual transformations, calculations, or operations performed on the data or the actual statistical methods employed to analyze the data differ from that stated in the protocol, a rationale for such deviation should be included.

10. Results

All data collected during the study must be summarized and analyzed (§58.185(a)(11)). The results for each protocol-defined variable used as evidence to support safety should be presented as text, tables or graphs (as appropriate). The exact location (appendix page numbers) of the supporting raw data should be referenced. Tables and graphs should be concise and user-friendly, since individual data will be located in the appendices.

11. Conclusions/discussion

An overall statement of the conclusions drawn from the analysis of the data regarding the target animal safety of the product must be included (§58.185(a)(11)). Furthermore, a description of all circumstances that may have affected the quality or integrity of the data must be included (§58.185(a)(9)). New or unexpected findings and their impact on the study outcome should be identified. Adverse events and their potential impact and any results, which may be inconsistent with the overall study conclusions, should also be discussed in detail.

12. Personnel

The name of the study director, the names of other scientists or professionals, and the names of supervisory personnel involved in the study must be included (§58.185(a)(10)).

13. Reports

The signed and dated reports of each scientist or other professional, e.g., pathologists and statisticians, involved in the study must be included (§58.185(a)(12)). Reports may be included in the Appendix.

14. QA Statement

A statement prepared and signed by the quality assurance unit as described in §58.35(b)(7) must be included (§58.185(a)(14)).

15. Location of specimens, raw data, and the final study report

The location where all specimens, raw data, and the final study report are to be stored must be included (§58.185(a)(13)).

16. Appendices

All study documentation should be included in the Appendices of the FSR. For a definition of study documentation, see the glossary of the guidance. Raw data should be submitted for all studies unless otherwise agreed upon with CVM.