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Guidance for Industry

ANESTHETICS FOR COMPANION ANIMALS

DRAFT GUIDANCE

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Additional copies of this draft guidance document can be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at <http://www.fda.gov/cvm>.

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Guidance for Industry Anesthetics for Companion Animals¹

This draft guidance, when finalized, will represent the agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance document makes recommendations to assist developers of general anesthetic drugs (injectable or inhalational) for use in companion animals (dogs, cats, and horses). The guidance discusses the contents of the target animal safety, effectiveness, and labeling technical sections of a new animal drug application (NADA) for general anesthetics.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

This guidance makes recommendations for the development of anesthetic new animal drug products for companion animals. The guidance specifically describes what should be considered while planning and executing safety and field studies for the proposed anesthetic. The following sections also include recommendations on how to analyze and package the collected data for submission to the Center for Veterinary Medicine (CVM).

You may follow the guidance document or may choose alternate procedures. It is recommended that you discuss your proposed study plans with CVM, especially if you choose to use alternate

¹ This guidance was prepared by the Office of New Animal Drug Evaluation, Division of Therapeutic Drugs for Non-Food Animals in the Center for Veterinary Medicine at the Food and Drug Administration.

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procedures. We would like to emphasize the importance of scheduling a presubmission conference with the appropriate division of CVM as you begin to make your investigational plans to ensure that you are completely informed on the requirements contained in the statute and regulations.

III. TARGET ANIMAL SAFETY

When developing a product for use in companion animals, it is critical to determine that the product can be used safely in the target animal (21 U.S.C. § 360b(d)(1)(B); 21 CFR § 514.1). Safety studies conducted in the laboratory should be carried out in compliance with FDA's good laboratory practices regulations (21 CFR Part 58) and should follow the principles outlined in CVM's *Target Animal Safety Guidelines* (#33). The type of general anesthetic being studied (for example, injectable, inhalational) will help determine what approach should be used to design and evaluate the safety studies. We recommend that sponsors discuss safety study designs with us and submit protocols for our review before initiating the studies.

In the following sections, we discuss exaggerated dose/duration studies (evaluating the safety of the anesthetic alone) and compatibility studies (evaluating safety of the anesthetic in the presence of preanesthetics).

A. Exaggerated Dose/Duration Safety Studies

The exaggerated dose/duration safety study evaluates the anesthetic alone in healthy animals. The purpose of this study is to identify adverse reactions and determine a safe upper limit for the anesthetic's recommended dose/duration. The use of exaggerated anesthetic doses could result in signs of such severity that little useful information is obtained. Excessive anesthetic doses may be fatal. We do not expect death to be an outcome of anesthetic safety studies. The margin of safety should be defined by clinical observations following toxic, but non-lethal doses. If anesthetic potency is such that the administration of exaggerated doses in the study results in severe clinical signs, you may consider appropriate alternatives such as increasing the number of anesthetic episodes (total excessive dose over time) or exaggerating the duration of anesthesia.

We recommend that you identify the appropriate doses for use in the safety study by evaluating a limited number of healthy animals that receive progressively increasing anesthetic doses (these may be pilot studies). Incremental increases in anesthetic dose are administered until a serious adverse reaction occurs. Examples of serious adverse reactions include apnea >120 seconds, HR <50 beats per minute, BP <60 mm Hg, potentially life-threatening ECG rhythms, potentially life-threatening clinical signs, or excessively prolonged recovery times. If you use the same group of animals for successive increases in anesthetic dose, anesthetic episodes should be separated by an adequate washout period to prevent carry-over effects. Once the appropriate exaggerated dose levels are identified, you should proceed to the exaggerated dose/duration safety study.

The following study designs are general examples. For exaggerated dose/duration safety studies, animals should be randomly assigned to treatment groups. We encourage you to consult with us

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during product development to determine the most appropriate study design for a particular product.

Injectable Anesthetics: To evaluate the induction dose, the following examples may be appropriate:

- Exaggerated dose: Treatment groups compare higher multiples of the induction dose to the recommended induction dose and to a control (traditional design).
- Exaggerated frequency of induction: Animals are anesthetized every other day for a period of days/weeks; the total anesthetic induction dose over time is measured.

If the injectable anesthetic is indicated for maintenance anesthesia, the study design should also reflect this, as in the following examples:

- Exaggerated number of maintenance injections: For anesthesia maintained by repeated bolus injections, the study evaluates the number of maintenance doses intended for the label as well as multiples of the proposed number of maintenance boluses (traditional study design).
- Exaggerated duration of maintenance by continuous rate infusion (CRI): For anesthesia maintained by continuous rate infusion, the study evaluates the intended duration and exaggerated durations of administration.

Inhalational Anesthetics

- Exaggerated dose: Treatment groups compare higher multiples of the vaporizer settings to the recommended settings and to a control (traditional study design).
- Exaggerated frequency: Animals are anesthetized every other day for a typical surgical duration over a period of days/weeks; the total anesthetic dose over time is evaluated.
- Exaggerated duration: Anesthesia is maintained for a typical surgical duration as well as multiples of this duration.

B. Compatibility Studies

Compatibility studies are controlled studies in which the proposed general anesthetic is evaluated prospectively in conjunction with other drugs commonly used as part of an anesthetic regimen. These generally include preanesthetics, other induction or maintenance anesthetics, and anticholinergic medications. The choice of appropriate drugs for compatibility studies should be determined by the current standard of veterinary anesthesiology.

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Before anesthesia, for most clinical procedures, one or more preanesthetic drugs are administered to calm, sedate, provide analgesia and/or provide muscle relaxation. Preanesthetic drugs can also decrease the amount of induction and/or maintenance anesthetic required, decrease salivation and airway secretions, and suppress vomiting and regurgitation.

Because the probability of a drug interaction increases with the number of drugs that a patient receives, the potential exists for undesirable drug interactions between the proposed anesthetic and other concurrently administered drugs. Compatibility studies identify safety issues associated with these interactions. Examples of typical preanesthetic/anesthetic effects that can be measured during compatibility studies include anesthetic dose sparing, changes in the quality of induction and recovery, as well as possible toxicity. You do not need to show that the concurrent use of the preanesthetic with the anesthetic provides additional benefits (synergism).

We encourage you to evaluate compatibility with a representative from each class of commonly used preanesthetics and anesthetics that could appropriately be used with the proposed anesthetic drug. Commonly used preanesthetic drug classes include phenothiazine tranquilizers, alpha₂-agonists, opioids, benzodiazepines, and anticholinergics. NSAIDS (nonsteroidal antiinflammatory drugs) are not referred to as preanesthetics within the scope of this guidance. Commonly used anesthetics include barbiturates, dissociatives, propofol, and inhalational agents.

We make the following recommendations with respect to anesthetic compatibility studies:

1. Study Design

We recommend that compatibility studies be conducted in the laboratory (instead of evaluation in field studies) because the controlled conditions minimize variability. Compatibility studies performed in a laboratory have the following benefits:

- Fewer animals are needed to provide usable results.
- Randomization of homogeneous animals to treatment groups is facilitated.
- More study designs are available (for example, crossover designs have the ability to use animals more than once, following suitably documented washout periods).
- Use of an anesthetic-only group for baseline measurements may be more acceptable.
- Well-controlled study conditions are easier to achieve.
- Use of concomitant medications that are not part of the anesthetic regime can be avoided.

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- Arterial systolic, diastolic, and mean blood pressure can be more easily and appropriately monitored.
- Invasive instrumentation/procedures can be used to provide more complete data, should they be needed.
- Anesthetic assessment procedures (for example, nonsurgical noxious stimulation) can be repeated at predetermined intervals.
- Investigator variability is more easily controlled.
- Consistent evaluation of adverse reactions (onset, duration, treatment, resolution) is easier to achieve.
- Complete necropsies can be performed on animals that die during the study.
- Adequate staffing can be assured for the evaluation of physiological variables.

Treatment groups can include more than one preanesthetic agent. A treatment group that evaluates the effects of the anesthetic alone provides baseline information. Appropriate clinical, physiologic, and anesthetic variables (see section V) should be compared among treatment groups to provide animal safety information. In addition to drug interactions, effects of special interest include anesthetic dose sparing, and changes in the quality of induction and recovery.

2. Evaluation of dose sparing effects

When a preanesthetic drug (for example, a sedative) exerts its effect concurrently with the general anesthetic, it may be appropriate to reduce the general anesthetic dose to maintain safe anesthetic conditions during induction, maintenance, and recovery. This anesthetic dose sparing results in balanced anesthesia, avoids anesthetic overdosage, and provides valuable safety information for labeling. Actual dose administered, induction time, duration of anesthesia, time to sternal recumbency, and time to standing recovery are useful measures of this effect. A treatment group evaluating the effects of the anesthetic alone provides comparative information. In the presence of a dose sparing preanesthetic, the desired levels of physiological variables are achieved at a reduced anesthetic dose. The appropriate reduced anesthetic dose is also reflected by satisfactory anesthetic scores for induction, maintenance, and recovery.

3. Choice of anesthesiology drugs for compatibility study

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Our preference is that the preanesthetics and other anesthetics chosen for the compatibility study are already approved with the appropriate indication in the target species. Each preanesthetic or additional anesthetic should be used according to its labeled indication (for example, prevent bradycardia, induce anesthesia). In some cases, a drug (usually preanesthetic), provides the desired effect but its approved labeling does not contain the appropriate indication. If the drug is commonly used by veterinarians and can be shown to reflect the standard of care in companion animals, then, for safety reasons, it should be evaluated in the presence of the proposed anesthetic. However, its extralabel use must meet the relevant requirements of 21 CFR Part 530. We also recommend that you explain the necessity for the drug's use based on a cogent, scientific rationale and document its common use in the field (as veterinary standard of care).

4. Anesthesiology drug doses in compatibility studies

The preanesthetic or additional anesthetic should be used at the approved labeled dose or current, scientifically valid, and documented clinical field dose. Some preanesthetics or other anesthetics are labeled for stand alone use (for example, for sedation). When used with the proposed anesthetic, the same drug could require an adjustment to its stand alone dose. A rationale for an adjusted dose could include information from preliminary studies, literature, formularies, or textbooks. We recommend that you discuss all preanesthetic or additional anesthetic doses with us before conducting the compatibility study.

It is important that preanesthetic effects are present before the induction of anesthesia so that balanced anesthesia is achieved. However, to prevent the introduction of variability into study results, we recommend standardizing the interval (within a time range) between the administration of preanesthetic and induction anesthetic.

5. Specific Safety Issues

The main safety studies may not evaluate all safety issues that should be addressed before marketing approval. Some examples of issues often not evaluated in safety studies include:

- Arrhythmogenicity of volatile inhalational anesthetics
- Risks associated with specific population subgroups
- Particular safety issues specific to a class of anesthetics
- Particular safety issues specific to the proposed anesthetic itself

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You can address these types of safety issues in various ways (for example, using exclusionary labeling comments, literature reviews, and/or additional studies).

IV. EFFECTIVENESS

The regulations at 21 CFR 514.117(b) describe the characteristics that are generally recognized as the essentials of adequate and well-controlled studies intended to demonstrate effectiveness and support the approval of a new anesthetic product or a new use of an approved anesthetic product. You should refer to these regulations when designing effectiveness studies.

In the following paragraphs, we discuss and make recommendations on key issues related to anesthetic effectiveness studies. We do not usually recommend placebo or active controls in effectiveness studies for anesthetic drugs. Each animal is either anesthetized or not anesthetized, as determined by the ability to intubate, by reflex responses, purposeful movements, and other clinical observations.

A. Dosage Characterization

Dosage characterization includes information on the dose or dose range, the dosing frequency, and the dosing duration. For inhalational anesthetics, minimal alveolar concentration (MAC) determination is considered part of dosage information and you should characterize it.

You need not provide dosage characterization as part of substantial evidence of effectiveness. You should, however, submit sufficient information to characterize the critical aspects of the dose response relationship. You may derive dosage characterization from dose titration studies, pilot studies, foreign studies, scientific literature, and assessments based on the modeling of pharmacokinetic and pharmacodynamic data.

The anesthetic maintenance dose (if appropriate for that anesthetic) should be characterized. Maintenance doses are administered by inhalation, by repeat bolus injections, or by continuous rate infusion (CRI). We encourage you to consider the following questions when designing studies to evaluate maintenance anesthesia using repeat bolus injections or CRI.

- How many times may the boluses be repeated or how long will CRI last?
- What is the rate of administration for a maintenance bolus or CRI?
- What types of procedures are indicated during maintenance of anesthesia using bolus injections or CRI?
- How frequently do boluses need to be repeated, or how are variations in the CRI rate determined?
- How are heart rate, blood pressure, respiratory rate, and other physiological variables affected when you give a maintenance bolus or change the rate of CRI?

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- Does the number of boluses, or the duration of CRI, affect recovery times? Is there any evidence of anesthetic accumulation (delayed recovery)?

B. Field Effectiveness Study

The purpose of a field study is to evaluate whether the proposed anesthetic is safe and effective for the target animal under the actual conditions of use according to its proposed indications. The field study confirms the dosage and provides additional information to that obtained from the compatibility study in the intended patient population.

Field studies, whether conducted in the United States or in other countries, should use the same drugs and standard of veterinary practice as in the United States, according to an acceptable protocol. All study data and reports must be submitted in English (21 CFR 514.110(b)(1)). We recommend reporting data in units commonly used in the United States. We also recommend that procedures conducted under anesthesia are similar to those commonly performed in the United States.

1. Evaluation of Subpopulations

The field study provides safety and effectiveness information in the target animal and may also include some data generated in specific subpopulations (for example, juveniles, geriatric animals, sighthounds, and animals with compromised cardiovascular, renal, or hepatic function). If the field study does not provide substantial evidence of effectiveness to adequately assess the effects of the anesthetic within a significant subpopulation (usually because there are inadequate numbers of cases within the subpopulation), we may require product labeling to exclude certain subpopulations (for example, ...the use of the anesthetic has not been evaluated in foals, pregnant animals, puppies, or geriatrics.)

2. Treatment Groups

We encourage the inclusion of a representative of each class of preanesthetic (for example, opioid, alpha₂-agonist, phenothiazine tranquilizer, benzodiazepine) in treatment groups. You may include more than one preanesthetic in a treatment group. When clinically acceptable, we encourage you to evaluate the anesthetic alone (in the absence of preanesthesia) to provide baseline information.

Depending on the indication, it may be necessary to evaluate an anesthetic in the presence of other anesthetics. If the proposed anesthetic requires evaluation with other induction agents, treatment groups should include an appropriate representative of each class of induction agent commonly used in the target species (for example, barbiturates, dissociatives, propofol).

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To decrease variability and assist the formation of conclusions relative to anesthetic safety and effectiveness, we recommend that predetermined anesthetic regimens be defined in the protocol and that they reflect the standard of veterinary practice. The veterinarian (clinical investigator) then selects the appropriate anesthetic regimen that best meets each patient's needs within the limits of the protocol. In anesthetic field effectiveness studies, animals are usually assigned to treatment group by the clinician based on the nature of the clinical procedure rather than by randomization. The goal is not to compare treatment groups, but to evaluate the safety and effectiveness of the anesthetic in the presence of drugs contained in various regimens. The number of sites and procedures can be limited to decrease study variability and increase case numbers so that there are comparable groups of animals. During protocol review, we strongly recommend that you discuss the field study design so that each anesthetic regimen is represented by adequate numbers of cases within each group and at each location.

The decision to use an anticholinergic within each treatment group rests with the clinical investigator. When anticholinergics are used, we recommend that you clearly delineate the dose and timing of administration on the case report forms. You should compare cases treated with anticholinergics with those that do not receive anticholinergics within and across treatment groups.

3. Evaluation of Anesthetic Dose Sparing Effects

Dose sparing effects derived from laboratory compatibility studies should be confirmed in the field study. Actual dose administered, induction time, duration of anesthesia, time to sternal recumbency, and time to standing recovery are useful measures of this effect. Physiological measurements should be acceptable during anesthesia and the desired procedure should be satisfactorily accomplished. If clinically appropriate, a treatment group evaluating the effects of the anesthetic alone provides comparative information for these variables.

V. RECOMMENDED VARIABLES FOR SAFETY AND EFFECTIVENESS STUDIES

Variables that are not specifically related to anesthetic evaluation, may not be represented in this section (for example, signalment, physical examinations, clinical pathology, necropsy, pharmacokinetic). Physical examination results should be recorded on forms according to organ systems. Injection sites, whether intravenous, subcutaneous, or intramuscular, should be grossly and histologically evaluated in safety studies, and clinically evaluated in field studies. The following anesthetic related variables should be measured in anesthetic safety and effectiveness studies; however, the inclusion of study variables may vary between field and laboratory settings.

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A. Clinical Variables	<ul style="list-style-type: none">• ability to intubate• purposeful movements• response to noxious stimuli at predesignated intervals (for example, tail clamp, thermal stimuli)• muscle relaxation
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B. Physiologic Variables	<ul style="list-style-type: none">• systolic, diastolic, and mean arterial blood pressure• blood gas analysis (partial pressure of oxygen, partial pressure of carbon dioxide, total carbon dioxide, pH, bicarbonate concentration)• K^+, Ca^{++}, other electrolytes• end tidal CO_2• pulse rate (PR)• respiratory rate (RR)• mucous membrane color (mm)• body temperature (T)• percent oxygen hemoglobin saturation (O_2 sat)• cardiac rhythm measured by electrocardiogram (ECG)
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C. Anesthetic Variables	<ul style="list-style-type: none">• induction time (beginning of anesthetic administration to intubation)• duration of anesthesia (time from intubation to extubation)• recovery:<ul style="list-style-type: none">-extubation to initial purposeful movement-extubation to sternal recumbency-extubation to standing recovery• anesthetic performance:<ul style="list-style-type: none">-quality of anesthetic induction-quality of anesthetic maintenance-quality of anesthetic recovery• for inhalational anesthetics:
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	<ul style="list-style-type: none">-vaporizer concentration and flow rates during induction and maintenance-total volume per anesthetic episode (mL)-occurrence, number, and reasons for changes in vaporizer settings-spontaneous breathing of room air or positive pressure ventilation <ul style="list-style-type: none">• for injectable anesthetics:<ul style="list-style-type: none">-dose of anesthetic for induction (mg, mL, mg/kg)-dose of anesthetic for maintenance (mg, mL, mg/kg)-duration of anesthesia per injection (min)-duration of bolus dose administration (seconds)-number of bolus injections used for maintenance-maintenance using continuous infusion (mg, mL, mg/kg/min <u>and</u> mL/kg/minute)• administration of supplemental oxygen (duration, reason, frequency, stage of anesthesia)
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VI. ADVERSE REACTIONS

A. Adverse Reactions During Safety And Effectiveness Studies

You must promptly investigate and report to FDA any findings associated with the use of the new animal drug that may suggest significant hazards pertinent to the safety of the new animal drug (see 21 CFR 511.1(b)(8)(ii)). For all studies that you conduct, you should provide information on adverse reactions in the final study report. You should provide detailed descriptions of adverse reactions, including the following:

- Description of the adverse reaction
- Anesthetic phase when the reaction was observed (induction, maintenance, recovery)
- Duration
- Treatment, if given
- Outcome
- Relationship to administration of the proposed anesthetic
- Likelihood of a drug interaction with the proposed anesthetic

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- Type, quantity, and duration of concomitant medications/therapies
- Clinical pathology
- Necropsy results
- Other

We recommend that you organize descriptions of adverse reactions by body system:

Examples of organ systems		
Cardiovascular	Neurologic	Integumentary/Dermatologic
Respiratory	Renal	Other
Hepatic	Gastrointestinal	

We strongly recommend that you look for associations between adverse reactions and the results from clinical, physiological, and anesthetic variables in the final study report.

Terms such as “side effects,” “expected” adverse events, or “problems beyond usual clinical experience” are confusing and inappropriate for evaluation of an anesthetic. It is helpful to define some of the adverse reactions of greatest concern in advance using specific parameters. The following definitions are given as examples that may change according to the species, drug, and type of study:

- apnea of ≥ 120 seconds
- heart rate of ≤ 50 beats per minute
- mean indirect arterial blood pressure of ≤ 60 mm Hg
- potentially lethal ECG rhythm or adverse clinical signs during anesthesia
- mean oxygen saturation of $<80\%$ (any duration) or $<90\%$ for ≥ 3 minutes
- death

B. Adverse Reaction Reports From Other Countries In The Target Species

For anesthetic agents, we are interested in adverse reaction reports for anesthetics already approved and marketed in countries other than the United States. The regulations require the submission of this information (21 CFR 514.1(b)(8)(iv)). Information on the number of doses sold (by year, by country, etc.) should be provided to give context to the number of adverse reaction reports. We recommend tabulating all information so that results may be easily compared.

Tabulated information should include dose delivered (label dose or overdose), concurrent medications, and outcome (death, recovery). Deaths should be classified as anesthetic related or deaths with an undetermined causal relationship to the anesthetic. You should include individual

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case reports (if available) for animals that died and for those showing severe or unusual adverse reactions, with a summary of clinical pathology and/or necropsy results.

We recommend tabulating adverse reactions by organ system. We also recommend that you break down the adverse reactions into subcategories based on clinical signs. For example, you could divide large numbers of cases having adverse respiratory signs into subcategories, such as apnea, respiratory acidosis, and inadequate oxygen saturation.

C. Adverse Reaction Reports From Humans

If an anesthetic is already approved for use in humans (in the United States or elsewhere), we recommend that you submit the most recently approved package insert for the human product, accompanied by an update on safety issues associated with the use of the approved human anesthetic (reports of human adverse events since approval).

VII. OTHER CONSIDERATIONS

The following sections discuss key issues related to the design, performance, and evaluation of safety and effectiveness studies, with comments on the submission of data to CVM in study reports for approval of anesthetics for companion animals.

A. Data Presentation in the Final Study Report (FSR)

The preparation of a final study report is a required component of an adequate and well-controlled study. The required characteristics of an adequate and well-controlled study are described in 21 CFR § 514.117(b). The final study report should be a comprehensive, stand-alone document. It must provide a clear explanation of the study objectives, experimental materials and methods, and a presentation and critical scientific evaluation of the results. The final study report should be written when collection of all raw data for that study is complete. CVM's guidance for industry #104 provides recommendations for the content of the final study report in detail.

All data collected during a study should be summarized and analyzed. A description of how the results for each protocol-defined variable support effectiveness or safety should be included. We recommend that you analyze certain variables (for example, clinical pathology) for statistically significant differences between treatment groups. This analysis is not unique to anesthetics (see CVM guidance for industry #33). Results should be presented using text, with tables and graphs.

We recommend that you present data in tables containing individual animal results and in summary tables for each variable (descriptive statistics). Summary tables should include means, ranges, and standard deviations for each variable. Additionally, it is useful to stratify summary tables simultaneously according to treatment group and sex. Tables can be further stratified by dose for intramuscular anesthetics or anesthetic bolus injections. An identification key should accompany the report to define any abbreviations used in

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data tables. You can use graphs to present data, along with the tables from which they are derived.

We recommend that you thoroughly discuss the information in the data tables in the final study report. For each individual animal, you should explain the interrelationship of clinical signs, physiological data, anesthetic variables, subjective quality assessments, and adverse reactions, etc. In a similar manner, you should discuss the information in the summary tables and evaluate relationships between all variables among treatment groups and important population subgroups (for example, breed, gender, age, health status, etc.). In addition, you should discuss the association of treatment, time, procedure, dose, or other conditions with the occurrence of adverse reactions.

Presentation of descriptive statistics will help determine anesthesia times (for example, time to induction, length of recovery with and without preanesthetic administration) for inclusion in labeling. Anesthesia time intervals should be presented for the anesthetic when used alone (if appropriate), used concurrently with preanesthetics, and used with other induction and maintenance anesthetics. Dose information based on descriptive statistics should describe dose sparing effects among treatment groups and important population subgroups.

The final study report should contain the conclusions drawn from the analysis of the data. 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 that are inconsistent with the overall study conclusions, should also be discussed in detail.

B. Anesthetic Labeling

The package insert should include certain labeling information unique to anesthetics. In this section of the guidance, we discuss several examples and provide some proposed wording.

1. Dosage and Administration Section

The Dosage and Administration section should include safety recommendations related to anesthetic dose sparing effects. Examples of labeling statements regarding dose sparing follow:

- *When used with opioid, alpha₂-agonist, etc. premedication, the anesthetic dose should be decreased by approximately x amount.*
- *The dose of anesthetic is not affected by anticholinergic premedication.*

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- *Anesthetic induction dosages administered with premedication ranged from ..to..*
- *Anesthetic induction dosages administered without premedication ranged from ..to..*

Safety recommendations on the use of the proposed anesthetic in the presence of typical preanesthetics should refer to preanesthetic drug classes, rather than specific preanesthetic drugs.

You should include a statement (if supported by your data), such as the following, in the Dosage and Administration section of the label:

Premedication: No specific premedication is either indicated or contraindicated with [the proposed anesthetic]. The necessity for, choice of, as well as any necessary reduction of dose for the premedicant, is left to the discretion of the veterinarian.

This statement should be followed with current references for the selected doses (for example, a textbook or formulary).

2. Target Animal Safety Section

The Target Animal Safety section of the package insert should discuss drug interactions providing information on the safe use of the proposed anesthetic with at least one representative from each preanesthetic and anesthetic drug class. The following are examples of typical labeling statements regarding drug interactions:

If the proposed anesthetic is inhalational, a statement should describe its safety with injectable anesthetics.

*[Proposed inhalational anesthetic] is compatible with barbiturates, propofol, dissociatives anesthetics, **and/or** other commonly used injectable anesthetics.*

If the proposed anesthetic is injectable, a statement should describe its safety with other inhalational anesthetics.

[Proposed injectable anesthetic] is compatible with commonly used halogenated volatile inhalational anesthetics.

For **all** proposed anesthetics, the following statement can be used to describe its safety with classes of preanesthetics:

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[Proposed anesthetic] is compatible with benzodiazepines, opioids, alpha₂-agonists, and phenothiazines as commonly used preanesthetics in surgical practice.

3. Contraindications, Warnings, and Precautions, Sections

The Contraindications, Warnings, and Precautions sections of the package insert should also provide statements about premedicant/anesthetic safety. These statements should be based on preapproval study data, human or veterinary package inserts for similar products, scientific literature, and/or other sources.

The Warnings section should contain information on human user safety when there is evidence of an association of a serious hazard with a drug. Warning statements should also refer to human use or accidental exposure. Various examples of labeling statements regarding human user safety follow:

- For inhalational anesthetics:

Operating rooms and animal recovery areas should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors. Symptoms of human overexposure (inhalation) to vapors include respiratory depression, hypotension, bradycardia, shivering, nausea, and headache. If these symptoms occur, remove the individual from the source of exposure and seek medical attention.

The National Institute for Occupational Safety and Health (NIOSH) recommends an 8 hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general.

- For injectable anesthetics:

[The proposed anesthetic] should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting.

Exercise caution to avoid accidental self-injection. Overdose is likely to cause cardiorespiratory depression (such as hypotension, bradycardia, and/or apnea). Remove the individual from the source of exposure and seek medical attention.

Rare cases of self-administration have been reported, including fatalities in humans.

C. Liability Assessment for Product Abuse

The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, requires that the Secretary of the Department of Health and Human Services (HHS) make a recommendation for scheduling to the Drug Enforcement Administration

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(DEA) for any drug that has abuse liability (21 U.S.C. §§ 811 and 812). The FDA's Controlled Substance Staff (CSS) performs the scientific evaluation of the abuse liability of a drug.

Early in the drug development process, you should contact the CSS in FDA's Center for Drug Evaluation and Research. The CSS will help you identify what information should be included in the abuse liability assessment package, which is submitted directly to the CSS. The CSS evaluates whether the drug needs to be scheduled under the CSA and/or have other warnings relative to human abuse and dependence placed in its labeling. If necessary, the CSS makes a drug scheduling recommendation to the Drug Enforcement Administration (DEA). Examples of information that should be submitted in the abuse liability assessment package include:

- A description of the drug's chemical structure and class, formulation, pharmacology, biochemical profile, chemistry, pharmacokinetics, and adverse reactions
- A summary of available safety and effectiveness data, including information on overdose
- Data on actual use, abuse, and misuse, including fatalities, hospital emergency reports, and suicides/suicide attempts
- A sponsor-proposed schedule for the drug

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GLOSSARY

The following definitions are presented for use with this guidance document.

Anesthetic Regimen: A selection of premedicants (analgesics, sedatives, tranquilizers, anticholinergics) used with a general anesthetic to achieve balanced anesthesia.

Balanced Anesthesia: An anesthetic experience of maximal safety and effectiveness achieved by adjusting the presence and the amounts of various preanesthetics with induction and maintenance general anesthetics.

Compatibility Study: The compatibility study defines safety issues including preanesthetic dose sparing effects in a controlled study in which the proposed general anesthetic is evaluated prospectively in conjunction with preanesthetics identified by the current standard of veterinary anesthesiology.

Continuous Rate Infusion (CRI): CRI is continuous injection of the dose of a drug directly into a vein over time, usually to maintain anesthesia, using some method of infusion. The dose is usually expressed in terms of mass and time (for example, mg/min or g/hr), or mass per unit of body weight per unit of time (for example, mcg/kg/min).

Dose Sparing Effects: The reduction of anesthetic dosage that may occur when a preanesthetic drug (for example, a sedative) exerts its effect concurrently with that of the general anesthetic. The reduced anesthetic dose is used to maintain safe anesthetic conditions during induction, maintenance, and recovery.

Minimal Alveolar Concentration (MAC): A standard of comparison for potency of general anesthetics. The alveolar concentration of an inhalational anesthetic at which 50 percent of healthy patients fail to respond to surgical stimuli (for example, an incision) is 1 MAC. Multiples of MAC are used as a guide for surgical levels of anesthesia, which are typically 1.3 to 1.5 times the MAC value.

Preanesthetics (premedicants): Drugs administered before anesthesia to prepare the patient for anesthesia and contribute to balanced induction, maintenance, and/or recovery. Preanesthetics may calm, sedate, provide analgesia, cause muscle relaxation, decrease anesthetic requirements, decrease salivation, decrease airway secretions, and/or suppress vomiting and regurgitation.