J-E-BQ eSubmitter Template

Note that this template relies on information obtained in the separate eSubmitter "7.0 Product Description" tab.

When answering the following questions, it is important to answer each question in its entirety. The information you provide in the QbR template should be able to stand alone; therefore, it is not appropriate to reference other versions of a protocol in your QbR answers. Protocol concurrence will be issued solely based upon the information you provide in the QbR template. Please contact CVMDGADMGT@fda.hhs.gov with any questions.

Template questions are written in **bold text**
Hints for the user are designated by HINT: text
Programming instructions are provided by *<italics text>*
Upload prompts are indicated by ***Upload: text***

Table of Contents

1.0 GENERAL INFORMATION

(Use SI units in any responses where units are requested)

What type of protocol are you submitting?
HINT: if you are submitting a blood level bioequivalence study protocol, please note that eSubmitter should only be used for submission of protocols for routine blood level bioequivalence studies. Please contact CVM prior to submitting your QBR responses through the eSubmitter gateway if you are planning a blood level bioequivalence study that involves:

- use of any alternate study design (including adaptive design),
- dosing of animals multiple times during each period, or
- Type A medicated articles.

<User to select one of the following from a pull down list:>

- **Blood Level Bioequivalence Study;**
  - *<If "Blood Level Bioequivalence Study" is selected:>*
    What is the design of your Blood Level Bioequivalence Study?
    <User to select one of the following from a pull down list:>
    - **Crossover (including RSABE analysis) or Parallel Design;**
      - *<If "Crossover (including RSABE analysis) or Parallel Design" is selected: all Sections that follow will populate in their entirety except for 32.0 Protocol>*
    - **Alternate Design (including adaptive design)**
      - *<If "Alternate Design (including adaptive design)" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*
- **Clinical Endpoint Study;**
  - *<If "Clinical Endpoint Study" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*
- **Pharmacological Endpoint Study;**
  - *<If "Pharmacological Endpoint Study" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*
- **Palatability Study;**
  - *<If "Palatability Study" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*
- **Dissolution Study;**
  - *<If "Dissolution Study" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*
- **Analytical Methods;**
  - *<If "Analytical Methods" is selected: the remainder of 1.0 General Information populates, followed by abbreviated 4.0 Protocol Background Information, 32.0 Protocol (allowing protocol upload), and 33.0 Comments>*

- **Other (Unclassified Study)**
  - **If Other; Unclassified is selected, please specify:** *<Click here to enter text. 40 characters>*

Study/Trial ID: *<Click here to enter text. 40 characters>*

Is the submitted protocol for a study that FDA and you consider to be an essential part of the basis for making the decision to approve or not approve an original or supplemental ANADA?
- **YES**
- **NO**

Are you requesting protocol review and concurrence from CVM?
- **YES**
- **NO**

Is this submission in response to a CVM Protocol Non-Concurrence Letter?
- **YES**
  - **If Yes, please enter the CVM Submission Number:** *<Click here to enter text. 4 characters>*
- **NO**

<The following question is only enabled for Blood Level Bioequivalence Studies:>
What is the status of the bioanalytical methods submission?
HINT: select one of the following options.
- **Analytical methods have been submitted to CVM and found acceptable**
  - *<Enter the submission number: Click here to enter text. 250 characters>*
- **Analytical methods have been submitted to CVM and are under review**
  - *<Enter the submission number (if known, otherwise enter "TBD"): Click here to enter text. 250 characters>*
- **Analytical methods have not been submitted to CVM**

Has a suitability petition been granted for the proposed generic product?
- **YES**
  - *<If "YES":>* **Provide the suitability petition number, the date on which it was granted, and a description of the applicable change(s):** *<Click here to enter text. 500 characters>*
- **NO**

<The following question is only enabled for Blood Level Bioequivalence Studies, Crossover (including RSABE analysis) or Parallel Design>
- **Confirm agreement: The information entered into eSubmitter during this question-based process is consistent with the language in the protocol that will be used to conduct the study at all facilities (excluding documented amendments or deviations).**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

2.0 REFERENCE ARTICLE

The following information, as provided, will be evaluated in conjunction with the Reference Listed Product Details that were already provided in the Product Description tab.

Dosage form and concentration/strength of the reference article to be used in the study. *<Click here to enter text. 250 characters>*

List all of the concentrations/strengths approved for the reference product:
<Click here to enter text. 500 characters>

Select the following commitment statements regarding the reference article.
HINT: Select ALL of the statements for which the sponsor confirms agreement. If a statement is not selected, an explanation and justification must be provided below.

- **The final formulation of the FDA approved reference article will be used in this study.**
- **The lot number and expiration date of the reference article used in the study will be provided in the final study report.**
- **The reference article will be handled and shipped under labeled storage conditions.**
- **The shipping conditions and receipt of the reference article will be documented and provided in the final study report.**

If you have not selected all of the above statements, provide an explanation and justification for that choice:
<Click here to enter text. 1000 characters>

3.0 TEST ARTICLE

The following information, as provided, will be evaluated in conjunction with the Product Description Details that were already provided in the Product Description tab.

Dosage form of the generic test article to be used in the current study:
HINT: The list below is populated with the dosage form designations you provided in the Product Description tab. Please select which of these dosage forms will be used in the study.
<User will be able to select from dosage form designations provided in the product description tab.>

Concentration/strength of the generic test article to be used in the study:
<Click here to enter text. 100 characters>

If there are multiple proposed concentrations/strengths for the proposed generic product, briefly describe how you intend to obtain approval for the proposed concentrations/strengths that will not be used in the blood level bioequivalence study (*This may include in vitro* dissolution testing or multiple *in vivo* studies.): HINT: Enter "N/A" if not applicable.
<Click here to enter text. HTML question>

Select the following commitment statements regarding the test article.

HINT: Select ALL of the statements for which the sponsor confirms agreement. If a statement is not selected, an explanation and justification must be provided below.

- **The final formulation of the test article will be used in this study.**
- **The lot number, expiration or manufactured date, and certificate of analysis (COA) of the test article used in the study will be provided in the final study report.**
- **The potency of the test article will be analyzed, and will be used in the study only if it is found to be within +/- 5% of the assay or label claim of the reference article. Details of the analysis are not required for protocol concurrence. Analysis details will be required in the final study report as part of the COA.**
- **The test article will be handled and shipped by a carrier under the appropriate storage conditions to the test facility.**
- **The shipping conditions and receipt of the test article will be documented and provided in the final study report.**

If you have not selected all of the above statements, provide an explanation and justification for that choice:
<Click here to enter text. 1000 characters>

4.0 PROTOCOL BACKGROUND INFORMATION

<Only the first two items in Section 4.0 are enabled if a protocol type other than a Blood Level BE Study/ Crossover (including RSABE analysis) or Parallel Design>

Protocol title:
HINT: Enter the title of the protocol.
<Click here to enter text. 500 characters>

Version number of protocol: *<Click here to enter text. 100 characters>*

Protocol number(s):
HINT: Enter the facility and/or sponsor protocol number(s).
<Click here to enter text. 100 characters>

Describe the protocol objective.
HINT: The objective should include your intent to assess the bioequivalence of the generic test article with the reference listed new animal drug (RLNAD). Include the intended species, test article, RLNAD/control article and dose in this section.
<Click here to enter text. HTML question>

Describe the study personnel.
HINT: Enter the name, credentials, and the address/affiliation of the following study personnel. If the information has yet to be determined, enter "TBD".

- **Study director:** *<Click here to enter text. 100 characters>*
- **Sponsor representative:** *<Click here to enter text. 100 characters>*
- **Study veterinarian:** *<Click here to enter text. 100 characters>*
- **Test facility management:** *<Click here to enter text. 100 characters>*
- **Test facility quality assurance:** *<Click here to enter text. 100 characters>*
- **Bioanalytical facility quality assurance:** *<Click here to enter text. 100 characters>*

- **Bioanalytical facility principle investigator:** *<Click here to enter text. 100 characters>*
- **Statistician:** *<Click here to enter text. 100 characters>*
- **Other:** *<Click here to enter text. 500 characters>*

Where will the study be conducted?
HINT: Enter the requested information. If the information has yet to be determined, enter "TBD".

- **Test facility name:** *<Click here to enter text. 100 characters>*
- **Test facility address:** *<Click here to enter text. 250 characters>*
- **Bioanalytical facility name:** *<Click here to enter text. 100 characters>*
- **Bioanalytical facility address:** *<Click here to enter text.250 characters>*
- **Additional facility names and addresses:**
  HINT: Enter "N/A" if not applicable.
  <Click here to enter text. 250 characters>

5.0 REGULATORY STANDARDS

What are the study standards?
HINT: Indicate if the study will be conducted in accordance with each of the following standards or with respect to the GFI documents, in accordance with the recommendations outlined in the GFI. If "NO", provide the information requested.

- **Good Laboratory Practices (GLP) 21 CFR Part 58:**
  - **YES**
  - **NO**
    - *<If "NO":>* **List and justify all alternate standard(s) (e.g., OECD) that will be used:** *<Click here to enter text. 1000 characters>*
- **CVM Guidance for Industry (GFI) #35, Bioequivalence Guidance, and/or CVM GFI #224 (VICH GL52), Bioequivalence: Blood Level Bioequivalence Study:**
  - **YES**
  - **NO**
    - *<If "NO":>* **Enter and explain how your alternative approach satisfies the requirement to demonstrate that your proposed generic new animal drug product is bioequivalent to the reference listed new animal drug (section 512(c)(2)(A)(vi) of the FD&C Act). Include in your explanation a discussion of your scientific justification for the alternative approach.** *<Click here to enter text. 1000 characters>*
- **FDA GFI #145, Bioanalytical Method Validation:**
  - **YES**
  - **NO**
    - *<If "NO":>* **Enter and explain how your alternative approach to bioanalytical method validation will ensure that you can satisfy the requirement to demonstrate that your proposed generic new animal drug product is**

bioequivalent to the reference listed new animal drug (section 512(c)(2)(A)(vi) of the FD&C Act). Include in your explanation a discussion of your scientific justification for the alternative approach. *<Click here to enter text. 1000 characters>*

- **Describe any additional standards to be used in the study.**
  HINT: Enter "N/A" if not applicable.
  <Click here to enter text. 1000 characters>

Confirm agreement:

- **The sponsor of this study will commit to providing to CVM a detailed description of all differences between 21 CFR Part 58 and the standards used in the study, as applicable to the study, including an assessment of the impact on the study for each difference.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

6.0 ANIMALS

Provide the following information about the test animals.
HINT: If an answer is unknown at this time or not applicable to the study, indicate this with "TBD" or "N/A".

- **Target animal(s) that will serve as test animals in the study:**
  HINT: The list below is populated with the target animal designations you provided in the Product Description tab. Please select which of these target animals will serve as test animals in the study.
  <User will be able to select from target animal designations provided in the product description tab.>
- **Breed, if applicable:** *<Click here to enter text. 100 characters>*
- **Justification for the intended species of use:** *<Click here to enter text. 1000 characters>*

7.0 HOUSING

Describe the conditions in which study animals will be housed for the duration of the study, including the acclimation period.
Upload: If available, UPLOAD a housing diagram pdf.
<Document upload is not required.>

- **Will the animals be individually housed during acclimation?**
  - **YES**
  - **NO**
    - *<If "NO":>* **Discuss alternate schema that will be used:** *<Click here to enter text. 1000 characters>*
- **Will the animals remain in the same housing environment (i.e., rooms, set of rooms, unit) after acclimation?**
  - **YES**
  - **NO**

        - *<If "NO":>* **Include details about when/how animals will be moved into housing assignments after acclimation:** *<Click here to enter text. 1000 characters>*
- **Will the animals be individually housed from the end of the acclimation through the final blood sampling time in the final period of the study?**
  HINT: If animals will be group housed (including horses comingled in a common paddock or pasture) at any time during this period (e.g., during washout or overnight), select "NO" and describe your housing plan.
    - **YES**
    - **NO**
        - *<If "NO":>*
            - **Discuss and justify any alternate schema that will be used:** *<Click here to enter text. HTML>*
            - **Describe treatment dispensation in animal enclosure, e.g. animals balanced by treatment sequence:** *<Click here to enter text.1000 characters>*
- **Provide a description of animal enclosures (e.g., type, size, raised flooring, shavings/bedding):** *<Click here to enter text. 1000 characters>*
- **Number of housing rooms for study animals and how they will be balanced:** *<Click here to enter text. 1000 characters>*
- **Describe how animal housing will be labeled:** *<Click here to enter text. 1000 characters>*

Confirm agreement:

- **Identifiable treatment information (e.g., treatment, treatment code, treatment sequence) will be excluded from animal housing labels**
    - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

Will study animals have any physical interaction with one another from the end of the acclimation through the final blood sampling time in the final period of the study?

- **YES**
    - *<If "YES":>* **Describe how animals will be chosen for physical interaction, and the physical interaction that will occur, including maximum hours per day:**
      HINT: Interaction should not occur during the interval between dosing and collection of the final blood sample for a given period:
      <Click here to enter text. 1000 characters>
- **NO**

Provide a description of environmental parameters (light/dark cycle, temperature, humidity, air changes): *<Click here to enter text. 1000 characters>*

Provide a description of cleaning and sanitation practices for animal housing rooms and enclosures, or provide reference to applicable study site SOP(s):
<Click here to enter text. 1000 characters>

8.0 FEED

Provide the following information regarding animal feeding practices during the study:

- **Feed type and amount:** *<Click here to enter text. 500 characters>*
- **If the diet provided is not a commercially available diet, provide details regarding plan for analysis of feed.**
  HINT: Enter "N/A" if not applicable.
  <Click here to enter text. 500 characters>
- **Feeding and fasting (if applicable) schedules [frequency and time(s)]**
  HINT: Provide details of the routine daily feeding schedule and any fasting schedule(s), if applicable. Include the timing and frequency for daily administration and removal of feed from animal housing units throughout the course of the study. Additionally, if animals will be fasted at any point in the study (including dosing days), include the timing for re-introduction of feed.
  <Click here to enter text. HTML Question.>

Confirm agreement:

- **Animal feeding practices will be documented throughout the course of the study. Daily feed delivery and consumption will be documented on an individual animal basis. Feed consumption may be recorded based on rough qualitative assessment (e.g., whole ration consumed/partial ration consumed/no ration consumed) that is performed upon removal of the previous day's leftover ration, if applicable. The corresponding data collection form (or blank screen shot of data input screen if using an electronic data capture system) will be uploaded in 31.0 Collection Forms.**
  HINT: Feed consumption/appetite is considered a general indicator of animal health and documentation of feed consumption history may be helpful in evaluating abnormal clinical observations and adverse events.
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm that animal feeding practices will be documented as described.** *<Click here to enter text.>*

9.0 WATER

How will water be provided to the study animals?
HINT: Provide details including water source, availability (e.g., *ad libitum*), and mechanism of delivery (e.g., automatic watering systems) for the provision of water to the study animals.
<Click here to enter text. 500 characters>

Will water be withheld from the study animals at any time during the study?

- **YES**
  - *<If "YES":>* **Provide a description of the protocol for withholding water from the study animals including the study days and**

times at which water will not be available to the study animals. Include a justification for withholding water from the study animals. *<Click here to enter text. 1000 characters>*

- **NO**

Provide details regarding the analysis of water. *<Click here to enter text. 500 characters>*

10.0 STUDY DESIGN

What experimental design will be used?
HINT: Select one of the following.

- **Crossover**
- **Parallel**

Describe the following study attributes.

- **Number of periods:** *<Click here to enter text. 100 characters>*
- **Number of treatment sequences:** *<Click here to enter text. 100 characters>*
- **Description of treatment sequences:**
  HINT: e.g., Reference - Test, Test - Reference
  <Click here to enter text. 500 characters>
- **Number of animals in each sequence:** *<Click here to enter text. 100 characters>*

What is the plasma terminal elimination half-life of the drug?
<Click here to enter text. 500 characters>

What will be the washout period?
HINT: The washout period should be of sufficient duration to assure there is no residual drug from one period of the study impacting blood levels in another period of the study. CVM recommends that the washout period be at least 5 times the terminal elimination half-life after the peak plasma concentration, and sufficient to allow for blood volume replenishment of test animals.
<Click here to enter text. 500 characters>

Provide justification for selected washout period.
HINT: Include how the chosen duration is sufficient to address drug elimination and replenish blood volume post-sampling from study subjects. If you are proposing a washout period different than the one recommended in the hint for the previous question, please explain how your alternative to the washout period will ensure that you can satisfy the requirement to demonstrate that your proposed generic new animal drug product is bioequivalent to the reference listed new animal drug (section 512(c)(2)(A)(vi) of the FD&C Act). Include in your explanation a discussion of your scientific justification for the alternative approach.
<Click here to enter text. 1000 characters>

Upload: UPLOAD a document containing any resources referenced in your justification for the selected washout period.
<Document upload is not required.>

Provide the following information regarding dose selection/dosage:

- **RLNAD label dosage:** *<Click here to enter text. 500 characters>*
- **Dosage to be used in the study:** *<Click here to enter text. 500 characters>*
- **Justification for selected dosage:**
  HINT: Include information regarding RLNAD label dosage, drug pharmacokinetics, and other factors as applicable.
  <Click here to enter text. 1000 characters>

11.0 RANDOMIZATION

Select the following commitment statements regarding randomization:
HINT: Select ALL statements to confirm sponsor's agreement with appropriate randomization.

- **Animals will be randomly assigned to treatment sequences.**
- **Animals will be randomly assigned to pen/cage (during acclimation and/or treatment phase of the study).**
- **Animals will be randomly assigned to the order animals are treated and samples collected (which may coincide with pen/cage randomization).**

Describe randomization method relevant to the three statements above, including who will perform randomization procedures, and on what study day(s):
HINT: Any restrictions to randomization should be discussed in this section. If using a random number generator, the method should be described (e.g., SAS PROC PLAN, Excel random number generator using a time-seed).

<If all three boxes above are NOT checked:> **Explain why you did not check all boxes associated with the commitment statements above.** *<Click here to enter text>*

Provide additional randomization details:

- **Describe any blocking or grouping of subjects.**
  HINT: Blocking is generally not necessary but may be justified, e.g., blocking by litter. Enter "N/A" if not applicable.
  <Click here to enter text. 1000 characters>
- **Describe any cohorts.**

HINT: Cohorts may be necessary due to facility or personnel constraints (e.g. housing in two rooms, staggering start dates). Cohorts should be balanced by treatment sequence. Enter "N/A" if not applicable.
<Click here to enter text. 1000 characters>

- **Describe any other randomization considerations.**
  HINT: Enter "N/A" if not applicable.
  <Click here to enter text. 1000 characters>

12.0 MASKING

How will masking be accomplished?
In most bioequivalence studies, complete separation of functions where only masked study personnel perform functions that may potentially impact study results or conclusions helps control bias.

- **Confirm agreement:**
  - **Separation of functions according to masking status will be used for controlling bias in the study.**
    - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above. If applicable, provide a description of the methods that will be used for controlling bias in the study.** *<Click here to enter text.>*

List the roles/titles of all personnel who will be unmasked (e.g., dosing technician). For each individual listed, provide a description of their involvement in study conduct and reason(s) for unmasking of that individual. *<Click here to enter text.>*

Confirm agreement:

- **All unmasked personnel listed above will not be involved in any of the following study activities: scheduled data collection; data corrections during the in-life and bioanalytical phases; decisions regarding animal care that are based on observations during the conduct of the study (i.e., modifications to treatment regimen, administration of concomitant medications or treatments); decisions regarding removal of animals after randomization that are based on observations during the conduct of the study.**
  HINT: Unscheduled clinical observations may be recorded by any study personnel as needed. For example, if an unmasked dosing technician observes an animal vomiting soon after dosing, they may record the observation.
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

Confirm agreement:

- **All study personnel not included in the list of unmasked personnel provided above will be masked.**

- *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

13.0 ACCLIMATION

Describe the procedure for acclimation of potential study animals to the conditions of the study.

- **Number of animals to be acclimated:** *<Click here to enter text. 100 characters>*
- **Duration of acclimation period:** *<Click here to enter text. 100 characters>*
- **List any sham procedures to enhance animal adjustment that will take place during acclimation (e.g., sham dosing, mock blood draws):**
  HINT: Enter "N/A" if not applicable.
  <Click here to enter text. 1000 characters>

14.0 BASELINE DATA

Check all procedures to collect baseline data that will be performed during the acclimation period. If known, provide the day on which the procedure is to take place.

- **Body weight determination:**
  - **YES**
    - *<If "YES":>* **Date(s)/Study Day(s) if applicable:**
      HINT: You may enter approximate date/study day ranges if exact date(s)/study day(s) are yet to be determined. If applicable, include information regarding repeat body weight determinations that will be performed throughout the course of the study.
      <Click here to enter text.100 characters >
  - **NO**
- **Complete blood count:**
  - **YES**
    - *<If "YES":>*
      - **Date(s)/Study Day(s) if applicable:**
        HINT: You may enter approximate date/study day ranges if exact date(s)/study day(s) are yet to be determined. If applicable, include information regarding repeat complete blood counts that will be performed throughout the course of the study.
        <Click here to enter text. 100 characters>
      - **What volume of blood will be collected from study animals for the purpose of performing this test?**
        <Click here to enter text.100 characters>
  - **NO**
- **Serum biochemistry:**
  - **YES**
    - *<If "YES":>*
      - **Date(s)/Study Day(s) if applicable:**
        HINT: You may enter approximate date/study day ranges if exact date(s)/study day(s) are yet to be determined. If applicable, include information regarding

repeat serum biochemistry measurements that will be performed throughout the course of the study.
<Click here to enter text. 100 characters>

- **What volume of blood will be collected from study animals for the purpose of performing this test?**
<Click here to enter text. 100 characters>

  - **NO**

- **Veterinary physical examination:**
  - **YES**
    - *<If "YES":>* **Date(s)/Study Day(s) if applicable:** HINT: You may enter approximate date/study day ranges if exact date(s)/study day(s) are yet to be determined. If applicable, include information regarding repeat veterinary physical examinations that will be performed throughout the course of the study.
<Click here to enter text. 100 characters>
  - **NO**
- **Describe any additional tests:**
HINT: Enter "N/A" if not applicable.
<Click here to enter text. 1000 characters>

15.0 INCLUSION CRITERIA

Describe the criteria for determining animal acceptability for study inclusion.

- **Age range:** *<Click here to enter text. 250 characters>*
- **Weight range, including units:**
HINT: An attempt should be made to restrict the weight to a narrow range.
<Click here to enter text. 250 characters>
- **Sex and reproductive status:**
HINT: Select all combinations of sex/reproductive status that may be used in the study.
  - **Female/Intact**
  - **Female/Neutered (Spayed)**
  - **Male/Intact**
  - **Male/Neutered (Castrated)**

Will the veterinarian be involved in determining if an animal is healthy enough for inclusion on the basis of the baseline data collected prior to study enrollment as described in the above section?

- **YES**
- **NO**
  - *<If "NO":>* **Provide an explanation and justification.** *<Click here to enter text. 1000 characters>*

List any additional criteria that will be used to determine an animal's eligibility for study inclusion.
HINT: Enter "N/A" if not applicable.
<Click here to enter text. 1000 characters>

16.0 EXCLUSION CRITERIA

Describe the criteria for which an animal may be excluded from study participation.

- **Restrictions on previous study enrollment:** *<Click here to enter text. 500 characters>*
- **Restrictions on recent medications/treatments:** *<Click here to enter text. 500 characters>*
- **Additional exclusion criteria:**
  HINT: List additional criteria that, if met, would disqualify an animal from study participation (e.g., clinically evident significant disease that would interfere with study objectives)
  <Click here to enter text. 1000 characters>

17.0 ENROLLMENT

How will animals be enrolled in the study?

- **Total number of animals to be enrolled in the treatment phase of the study:** *<Click here to enter text. 100 characters>*
- **Justification for the number of animals:**
  HINT: Pilot studies are recommended as a means of estimating appropriate sample size. Useful references for sample size estimates are included in GFI #224 (VICH GL52).
  <Click here to enter text. HTML question>
  - ***Upload: UPLOAD a document containing any resources referenced in your justification for the number of animals to be used in the study.***
    <Document upload is not required.>

For the case in which more animals are determined eligible based on inclusion/exclusion criteria than are required for study participation, describe the process by which animals will be selected for study enrollment.
<Click here to enter text. 1000 characters>

Describe any additional considerations regarding procedures for enrollment.
<Click here to enter text. 500 characters>

For each animal enrolled in the study, will all blood samples collected during completed periods (animal is successfully dosed and sampled at each planned time point) be assayed and included in statistical analysis for bioequivalence determination?

- **YES**
- **NO**
  - *<If "NO":>* **Describe and justify your alternative plan, including any additional randomization procedures that will be performed in order to make an a priori determination of the enrolled animal(s) for which samples from completed periods will not be assayed and included in statistical analysis for**

bioequivalence determination. *<Click here to enter text. 1000 characters>*

18.0 ANIMALS IDENTIFICATION

Describe the method of identification for animals used in the study.
HINT: CVM recommends two forms of identification. Describe all information that will be present on each form of identification (e.g., animal number, study number).
<Click here to enter text. 250 characters>

Confirm agreement:

- **Identifiable treatment information (e.g., treatment, treatment code, treatment sequence) will be excluded from animal identification devices (e.g., collars, tattoos).**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

19.0 DRUG ADMINISTRATION

- **Dose to be administered to test animals:** *<Click here to enter text. 250 characters>*
- **Route of administration of dose:**
  HINT: The list below is populated with the route of administration designations you provided in the Product Description tab. Please select which of these routes of administration is applicable to the study.
  <User will be able to select from route of administration designations provided in the product description tab.>

Confirm agreement:

- **Animals will be dosed at approximately the same time of day during each period.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above**. *<Click here to enter text.>*

Will the animals be in a fasted state at the time of dosing?
HINT: If the RLNAD label indicates the reference product is limited to administration either in the fed or fasted state, the study should be conducted accordingly.

- **YES**
  - *<If "YES":>* **Did you provide detailed information of the fasting schedule in your response in section 8.0 Feed?**
    - **YES**
    - **NO**
      - *<If "NO":>* **Provide a description of the fasting protocol, including dates and times at which food will be withdrawn and re-introduced.** *<Click here to enter text.>*
- **NO**

Provide a justification for the prandial state (fasted or not fasted) of study animals at the time of dosing.
HINT: This may include RLNAD administration information, and/or information on the drug formulation and pharmacokinetics, and whether feeding is expected to enhance or interfere with drug absorption.
<Click here to enter text. 1000 characters>

- ***Upload: UPLOAD a document containing any resources referenced in your justification for the prandial state of study animals at the time of dosing.***
  <Document upload is not required.>

How will the test and reference article be administered?

Provide a complete, step-by-step description of the method by which the dose will be prepared for administration. This should include the process(es) by which both the test and reference article will be removed from their packaging and prepared for individual dose administration. *<Click here to enter text. HTML question.>*

<If "route of administration of dose" was selected as "oral":>

- **Provide a complete, step-by-step description of the method by which the dose will be administered including any methods employed to ensure accurate and complete dose administration.**
  HINT: Any information pertaining to redosing in the case of a dosing failure (if applicable) will be requested later under the dosing failure and redosing section.
  <Click here to enter text. 1500 characters.>
- **Will a post-dose water flush be administered?**
  - **YES**
    - *<If "YES":>* **Describe the post-dose water flush including the volume of the flush and the method by which it will be administered:** *<Click here to enter text. 1000 characters>*
  - **NO**

<If "route of administration of dose" was selected as NOT "oral" (anything other than "oral"):>

- **Describe the exact anatomical location where the dose will be administered.** *<Click here to enter text. 500 characters>*
- **Provide a complete, step-by-step description of the method by which the dose will be administered including any methods employed to ensure accurate and complete dose administration.**
  HINT: Any information pertaining to redosing in the case of a dosing failure (if applicable) will be requested later under the dosing failure and redosing section.
  <Click here to enter text. 1500 characters.>

<If "route of administration of dose" was selected as "topical":>

- **Describe environmental factors (e.g., rain) taken into consideration in relation to dosing.**
  HINT: Enter N/A if not applicable.
  <Click here to enter text. 1000 characters>
- **Describe the procedure for monitoring for interference with drug absorption (e.g, animal licking application site), include the frequency of checks and who will perform checks.** *<Click here to enter text. 1000 characters>*

20.0 DOSING FAILURE AND REDOSING

For the purposes of a blood level bioequivalence study, any unforeseen issue or event that calls into question whether an animal received the intended treatment dose in a study period is considered a dosing failure. While it is not possible to provide for all possible scenarios which would result in a dosing failure, the following are examples for oral dosage forms: 1) technician or administrator error; 2) regurgitation within X minutes/hours of dosing; 3) vomiting within X minutes/hours of dosing. For injectable dosage forms, the following is an example: failure to provide the

entire dose volume into the intended tissue.

Describe, in detail, each individual circumstance (including timing of that circumstance) that would constitute a dosing failure (e.g., "subject vomits within 15 minutes of dose administration" or "subject vomits between 15 minutes and 3 hours of dose administration"). For each dosing failure circumstance, indicate if the animal will be redosed.
HINT: The decision to redose an animal should be based on the specific dosing failure situation and the pharmacokinetics (PK) of the drug product. For example, if an animal regurgitates or vomits within X minutes of dosing, even if the tablet is visible, a decision to redose should be made based on the PK of the drug. If the drug PK profile shows significant absorption at the X minute timepoint, it may not be prudent to redose.

Dosing Failure Circumstance *<(User to enter up to 10 rows)>*	**Redosing?**
<Click here to enter text. 1000 characters>	**YES or NO**
<Click here to enter text. 1000 characters>	**YES or NO**
<Click here to enter text. 1000 characters>	**YES or NO**
<Click here to enter text. 1000 characters>	**YES or NO**
<Click here to enter text. 1000 characters>	**YES or NO**

<For each "YES" to the redosing question above the following two questions will be enabled:>

- **Describe the procedure for re-dosing:** *<Click here to enter text. 1000 characters>*
- **Confirm agreement: Practices related to obtaining samples, assaying samples, and inclusion of pharmacokinetic data in statistical analysis for bioequivalence determination will be the same for animals that are successfully redosed as animals that were successfully dosed upon initial attempt.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

For any animal with a dosing failure, where redosing is not performed (or fails), provide the following information for the affected animal in the impacted study period.

- **Will blood sampling continue for the animal in the impacted study period?**
  - **YES**
    - *<If "YES":>*
      - **Provide justification for your answer.** *<Click here to enter text. 500 characters>*
      - **Will all samples collected for the impacted study period be assayed?**
        - **YES**
          - *<If "YES":>*
            - **Provide justification for your answer.** *<Click here to enter text. 500* characters>
            - **Confirm agreement: Data from the impacted period will not be included in the statistical**

analysis for determination of bioequivalence.
- *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

- **NO**

- **NO**
  - *<If "NO":>*
    - **Will the blood samples collected prior to the recognition of the dosing failure be assayed?**
      - **YES**
        - *<If "YES":>*
          - **Provide justification for your answer.** *<Click here to enter text. 500 characters>*
          - **Confirm agreement: Data from the impacted period will not be included in the statistical analysis for determination of bioequivalence.**
            - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*
      - **NO**

Select the following commitment statements regarding dosing failures.
HINT: Select ALL statements to confirm sponsor's agreement.

- **For any dosing failures, the following items will be documented at the time the dosing failure is observed: 1) a thorough and complete description of the dosing failure, 2) the determination of whether the associated animal will be re-dosed, and 3) the determination of whether sampling will continue for the associated animal during the impacted period and whether those samples will be assayed and the resulting data included in the statistical analysis for determination of bioequivalence. This documentation will be included in the final study report.**
- **When a dosing failure occurs prior to the last period of the study, the associated animal will be included in the subsequent periods of the study.**

<If both boxes above are NOT checked:> **Explain why you did not check both boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

21.0 SAMPLING

List the sampling time points relative to dosing. For each intended sampling time point, include the allowable time frame by which actual sampling time

may deviate from intended sampling time (e.g. +/- 2 minutes). *<Click here to enter text.>*

Justification for the sampling schedule, including reference to Tmax and plasma terminal elimination half-life: *<Click here to enter text.>*

- ***Upload: UPLOAD any documents or resources referenced in your justification for the sampling schedule.***
  HINT: It is not necessary to upload documents that have already been provided under the justification of the washout period.
  <Document upload is not required.>

Provide the following information regarding blood level sample collection and storage.

- **Sample collection site(s) (e.g., jugular vein):** *<Click here to enter text. 500 characters>*
- **Sampling method (e.gs. direct venipuncture, catheter):** *<Click here to enter text. 500 characters>*
- **Volume of sample:** *<Click here to enter text. 250 characters>*
- **Collection container (e.g., lithium heparin 5 mL vacutainer):** *<Click here to enter text. 250 characters>*
- **Specimen type to be analyzed (e.g., whole blood, plasma, serum):** *<Click here to enter text. 250 characters>*
- **Initial storage conditions:** *<Click here to enter text. 500 characters>*
- **Maximum amount of time samples will be maintained under initial storage conditions:** *<Click here to enter text. 500 characters>*
- **Centrifuge details, if applicable (include temperature, rpm, duration):** *<Click here to enter text. 500 characters>*
- **Aliquot information, if applicable:** *<Click here to enter text. 500 characters>*
- **Storage container including labelling information:** *<Click here to enter text. 500 characters>*

Confirm agreement:

- **Identifiable treatment information (e.g., treatment, treatment code, treatment sequence) will be excluded from storage container labels.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

Storage conditions prior to analysis: *<Click here to enter text. 500 characters>*

Confirm agreement:

- **Sample processing and handling will be consistent as described in the bioanalytical methods.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

Provide any details, as necessary, regarding shipment of samples from in-life test facility to bioanalytical test facility. *<Click here to enter text. 1000 characters>*

What is the analyte(s) [i.e., what is the compound(s) that you will be measuring to determine product bioequivalence]?
HINT: This information should be consistent with the information included in your analytical methods (H) submission. Please include the submission number for your analytical methods (H) submission if already submitted to CVM.
<Click here to enter text. 100 characters.>

22.0 CLINICAL OBSERVATIONS AND ADVERSE EVENTS

22.1 REGULAR CLINICALOBSERVATIONS

Regular clinical observations occur regularly (often daily) throughout the course of the study.

- **List the clinical parameters and abnormalities for which study animals will be regularly observed throughout the length of the study.**
  HINT: If your monitoring utilizes any scoring systems for evaluation (e.g., fecal scoring, mentation scoring) and the scoring system is not defined on the associated data collection form, include the scoring system definition (cut and paste table, if applicable).
  <Click here to enter text.>
- **Indicate the days on which regular clinical observations will be performed.**
  HINT: e.g., "Each study day between Study Day -7 and Study Day 16"
  <Click here to enter text. 500 characters>
- **Describe the timing/frequency of regular clinical observations.**
  HINT: e.g., "once daily" or "twice daily, at least 6 hours apart"
  <Click here to enter text.>
- **Describe the personnel that will be responsible for performing regular clinical observations.** *<Click here to enter text. 500 characters>*
- **Describe the processes for documenting regular clinical observations, and communicating abnormal observations to the veterinarian, study director and/or sponsor representative as necessary. Include the timeframe within which the veterinarian will be notified of abnormal observations (e.g., 24 hours, next business day).** *<Click here to enter text.>*

22.2 POST-DOSE CLINICALOBSERVATIONS

Post-dose clinical observations are additional clinical observations that occur during the period of time immediately following dosing.

- **List the clinical parameters and abnormalities for which study animals will be observed in the immediate post-dosing period.**
  HINT: For all dosage forms, this list should include vomiting, diarrhea, anorexia, and any additional abnormalities that are commonly observed as an adverse drug effect for the RLNAD. For oral dosage forms, this list should include regurgitation. For non-oral dosage forms, this list should include inflammation, irritation, and swelling. If the list of clinical parameters and abnormalities monitored are the same as the regular clinical observations (entered above), you may enter "same as regular clinical observations." If your monitoring

utilizes any scoring systems for evaluation (e.g., fecal scoring, mentation scoring) and the scoring system is not defined on the associated data collection form, include the scoring system definition (cut and paste table, if applicable).
<Click here to enter text.>

- **Describe the timing/frequency of post-dosing observations.** HINT: e.g., "hourly for the first six hours following dosing"
<Click here to enter text.>
- **Describe the personnel that will be responsible for performing post-dosing observations.** *<Click here to enter text. 500 characters>*
- **Describe the processes for documenting post-dosing observations, and communicating abnormal observations to the veterinarian, study director and/or sponsor representative as necessary. Include the timeframe within which the veterinarian will be notified of abnormal observations (e.g., 1 hour).** *<Click here to enter text.>*

22.3 ADVERSE EVENTS

Define adverse event in respect to this study. *<Click here to enter text. 1000 characters>*

Define serious adverse event in respect to this study. *<Click here to enter text. 1000 characters>*

Describe the process for intervention in the event of a serious adverse event. Include communication protocol between the veterinarian, study director and/or sponsor representative. Include the timeframe within which the veterinarian will be notified of serious adverse events (e.g., 1 hour). *<Click here to enter text. 1000 characters>*

Describe the process for documenting possible AEs. Define the role of the veterinarian, study director, and sponsor representative in classifying the severity of an adverse event and the likely relationship to test or reference article administration. Include any unmasking of masked personnel that may occur. *<Click here to enter text. 1000 characters>*

Confirm agreement:

- **All adverse events will be reported in the final study report.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.**
<Click here to enter text.>

23.0 CONCURRENT MEDICATION

Provide the following information regarding concurrent medication and treatment during the study.

- **Vaccinations, medications, nutraceuticals, or medical treatments are not anticipated to be needed during the study, and will only be administered under conditions of medical necessity as determined by a veterinarian.**

- **YES**
- **NO**
  - *<If "NO":>* **Provide a description of any treatments that are to be provided during the study.** *<Click here to enter text. 1000 characters>*

Confirm agreement:

- **If medications are provided to a study animal during the course of the study, and that animal is retained in the study, the following information will be included with the raw data: medication name, lot/batch number, expiration date, dose, frequency, route of administration and response to treatment.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

24.0 REMOVAL OF ENROLLED ANIMALS

Provide the following information regarding removal of enrolled animals from the study.

- **Describe the process by which an enrolled animal will be removed from the study, including: appropriate reasons for removal, persons with authority to remove animals from study, and disposition for removed animals.**
  HINT: If in section 12.0 Masking of this template you indicated that unmasked personnel will not be involved in decisions regarding the removal of enrolled animals, the response should be consistent with that information.
  <Click here to enter text.>
- **Describe the veterinarian's role regarding animal removal when animal welfare is a concern.** *<Click here to enter text. 1000 characters>*
- **For any animal that is removed from the study prior to completion of a sampling regimen, resulting in an incomplete period, will the blood samples collected during the incomplete period be assayed?**
  - **YES**
    - *<If "YES":>*
      - **Provide justification for your answer.** *<Click here to enter text. 500 characters>*
      - **Confirm agreement:**
        - **Data from incomplete periods will not be included in the statistical analysis for determination of bioequivalence.**
          - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*
  - **NO**
- **For any animal that is removed from the study following the completion of a period (e.g., animal completes Period 1 but is removed during Period 2), will blood samples collected during the completed period(s) be assayed and included in the statistical analysis for bioequivalence determination.**
  - **YES**
  - **NO**

        - *<If "NO":>* **Provide justification for why the data will not be used:** *<Click to enter text. 1000 characters>*
- **Select the following commitment statements regarding animal removal.**
  HINT: Select ALL statements to confirm sponsor's agreement.
    - **Reasons for all post-inclusion subject removal will be documented and included in the final study report.**
    - **Animals removed after the start of the treatment phase will not be replaced.**

  <If both boxes above are NOT checked:> **Explain why you did not check both boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

25.0 DATA MANAGEMENT

Provide the following information about how your data will be collected throughout the study.
HINT: Select all statements that are applicable.

- **Will you use paper forms to collect study data?**
    - **YES**
        - *<If "YES":>*
            - **Confirm agreement:**
                - **Exact copies of all raw data collected will be included with the Final Study Report and an electronic data file used for evaluation will be provided.**
                    - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*
    - **NO**
- **Will you use an electronic data capture system (EDCS) to collect study data?**
    - **YES**
        - *<If "YES":>*
            - **Discuss the EDCS and describe any additional data collection considerations:** *<Click here to enter text. 1000 characters>*
            - **Confirm the following will be included when you submit your data to CVM:**
                - **A statement that addresses the 21 CFR Part 11 compliance of the software.**
                - **A single, blank screen shot (PDF format) of each data form as it appears to the data collector.**
                - **An electronic copy of the data file that includes the audit trail.**

- **Copies of the program files used to generate the data files for evaluation/analysis (e.g. removing audit trail information, performing internal format changes).**

<If all boxes above are NOT checked:> **Explain why you did not check all boxes to confirm all items will be included in your data submission.** *<Click here to enter text.>*

- **NO**

Select the following commitment statements regarding re-assay and chromatograms.
CVM requires adequate justification when samples are repeat assayed. We do not accept reasons based on questionable pharmacokinetic results, i.e., a value is higher (lower) that expected based on the pharmacokinetic profile.
HINT: Select ALL statements to confirm sponsor's agreement.

- **Only samples with documented process or technician failure will be re-assayed.**
- **At least 20% of the chromatograms will be submitted to CVM with the Final Study Report.**
- **For re-assayed samples, the chromatogram for every analysis run will be submitted to CVM with the Final Study Report.**

<If all boxes above are NOT checked:> **Explain why you did not check all boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

Select the following commitment statements regarding how your data and programs will be submitted to CVM.
If necessary, electronic data files in other formats may be exactly copied, e.g., no column changes or calculations, using validated software. If files are converted, the program used to make the conversion should be provided to CVM. We encourage you to evaluate/analyze the data using the same file format that you submit to CVM. If you have questions, please contact CVM before sending in your submission.
HINT: Select ALL statements to confirm sponsor's agreement.

- **Data will be submitted in Extensible Markup Language (XML) or SAS XPORT Transport (XPT) file formats. Programs for data conversion, manipulation (e.g., calculation of PK parameters, transforming data) and analysis will be submitted in XML.**
- **The submission will include a ReadMe file, including a complete description of data file content and documented programs. For each data file, a list of all variables (full descriptive names), abbreviations if used, columns in the data file, and units of measure will be included. (Required for submission.)**
- **Any additional program files (e.g., randomization, for creation of graphs/tables) will be provided in XML.**

<If all boxes above are NOT checked:> **Explain why you did not check all boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

26.0 STATISTICAL METHODS

Confirm agreement:

- **The database will be locked for editing prior to data analysis by the unmasked statistician.**
  - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

What statistical methods will be used for determining bioequivalence?

- **Which of the following methods will you use to estimate AUC?**
  - **Trapezoidal rule, as outlined in GFI #35**
  - **Log trapezoidal estimation**
  - **Using a software package to calculate exact AUC**
  - **Other**
    - *<If "OTHER":>* **Describe method to calculate AUC and provide a justification for this method.** *<Click to enter text.>*
- **Which sampling times will be used in AUC estimation?**
  - **Nominal**
  - **Actual**

Will the following criteria for handling values below the lower limit of quantitation (LLOQ) in AUC estimation be used?

HINT: If the proposed product is an extended release formulation, "NO" should be selected and your alternative strategy for handling the values should be described below.

- **Values below the LLOQ will be assumed to be zero when they occur before the first observed value above the LLOQ. Values below the LLOQ will be set to missing when they occur between the first observed value above the LLOQ and before C_{max}. The first value below the LLOQ which occurs after C_{max} and all subsequent values, irrespective of whether they are below the LLOQ or not, will be set to missing.**
  - **YES**
  - **NO**
    - *<If "NO":>* **Describe how you will handle these values.** *<Click to enter text>*

<Visible message above following question:> **If you are evaluating bioequivalence for multiple analytes and are using alternative statistical analysis methods for any of the analytes, select "NO".**

For each analyte for which you are evaluating bioequivalence, will you analyze the data according to the description below?

- **Bioequivalence will be determined based on C_{max} and AUC. An Analysis of Variance (ANOVA) will be performed on natural log-transformed C_{max} and AUC using your proposed model without any degree of freedom adjustment. Treatment differences *(test article-reference article), with 90% confidence intervals, will be estimated using the within animal estimated error variances. The treatment differences and associated confidence interval boundary values will be back-transformed to provide point and interval estimates of the ratios of geometric means.***
  - **YES**
  - **NO**

<Visible message above following question:> **If you are evaluating bioequivalence for multiple analytes and are using alternative bioequivalence acceptance criteria for any of the analytes, select "NO".**

For each analyte for which you are evaluating bioequivalence, will you use the following criteria for determining bioequivalence?

- **The test and reference articles will be considered bioequivalent when the lower and upper back-transformed confidence limits for the pivotal parameters C_{max} and AUC are contained within the equivalence limits 0.80 to 1.25.**
  - **YES**
  - **NO**

<If both responses above are "YES"> **Describe the statistical model used for bioequivalence analysis in the study (take into account all relevant design and randomization restrictions).**
HINT: Refer to GFI#224, section III.A about the specific model and terms in the model (fixed-effect, random-effect, etc.) applicable to your study design.
<Click here to enter text. HTML>

<If both responses above are not "YES" (i.e., NO/NO, YES/NO, NO/YES)>
Describe your alternative approaches (e.g. RSABE), the statistical models (take into account all relevant design and randomization restrictions), and criteria for determining bioequivalence.
HINT: Refer to GFI#224, section III.A about the specific model and terms in the model (fixed-effect, random-effect, etc.) applicable to your study design.
<Click here to enter text. HTML>

Other data to support bioequivalence determination

- **Confirm agreement:**
  - **Mean values of T_{max} for test and reference articles will be calculated.**
    - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*

27.0 NECROPSY FOR STUDY PURPOSES

Provide the following information regarding necropsy of study animals.
HINT: Most studies will not include necropsy for study purposes as part of the study design.

- **Will animals be necropsied for study purposes?**
  - **YES**
    - *<If "YES":>*
      - **List the person(s) responsible for performing euthanasia of animals prior to necropsy.** *<Click here to enter text. 250 characters>*
      - **Provide a description of the method used to euthanize study animals prior to necropsy.** *<Click here to enter text. 1000 characters>*
      - **Describe the procedures for necropsying animals.** HINT: Include the person responsible for performing necropsy, the tissues to be collected, the storage details for tissue samples, the tests to be performed on samples, and any other relevant information. *<Click to enter text. 1000 characters>*
      - **Will necropsies be performed on one day?**
        - **YES**
        - **NO**
          - *<If "NO":>* **Indicate on which study days necropsies will be performed and how animals will be chosen for necropsy on each day and necropsy order:** *<Click here to enter text. 1000 characters>*
      - **Describe how necropsy order will be chosen (e.g. in cage order).** *<Click here to enter text. 500 characters>*
      - **Will one person be performing all necropsies?**
        - **YES**
        - **NO**
          - *<If "NO":>* **Indicate how many people will be performing necropsies, on which date(s)/study day(s), and for which animals:** *<Click to enter text 500 characters.>*

28.0 ANIMAL WELFARE

Provide the following information regarding euthanasia of study animals.

- **Confirm agreement:**
  - **Any animal with unrelieved pain or distress, moribund or terminally ill animal as determined by the study veterinarian and/or animal care and use committee will be euthanized by an acceptable or conditionally acceptable method according to the most current American Veterinary Medical Association Guidelines for the Euthanasia of Animals or similar document if the study is conducted outside of the United States.**
    - *<If box is NOT checked:>* **Explain why you did not check the box to confirm agreement with the statement above.** *<Click here to enter text.>*
- **Provide the method of euthanasia:** *<Click to enter text. 1000 characters>*
- **List the person(s) performing euthanasia:** *<Click to enter text. 250 characters>*
- If an animal is euthanized during the study for animal welfare concerns, will a gross necropsy be performed and if the cause of death is not apparent from gross necropsy, tissue samples collected and further testing pursued to determine cause of death (e.g., histopathology, microbiology)?
  - **YES**
  - **NO**
    - *<If "NO":>* **Explain and provide justification.** *<Click to enter text. 1000 characters>*

29.0 AMENDMENTS AND DEVIATIONS

Provide a definition of protocol amendment. *<Click here to enter text. 1000 characters>*

How will protocol amendments be handled?
HINT: Describe the processes by which:

- decisions regarding protocol amendments will be made;
- protocol amendments will be approved; and,
- protocol amendments (including the reason for the amendment and its perceived impact on the study) will be documented, and provided in the final report.

<Click here to enter text. 1000 characters>

Provide a definition of protocol deviation. *<Click here to enter text. 1000 characters>*

How will protocol deviations be handled?
HINT: Describe the process by which protocol deviations and their perceived impact on the study will be documented, and provided in the final report.
<Click here to enter text. 1000 characters>

30.0 FINAL STUDY REPORT

Select the following commitment statements regarding the final study report.
HINT: Select ALL statements to confirm sponsor's agreement.

- **The final study report will include, at a minimum, the elements outlined in 21 CFR Part 58.185.**

- **The final study report will be signed and dated by the study director.**
- **Corrections or additions to the final study report will be in the form of an amendment by the study director. The amendment will clearly identify that part of the final study report that is being added to or corrected and the reasons for the correction or addition, and will be signed and dated by the person responsible.**

<If all boxes above are NOT checked:> **Explain why you did not check all boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

31.0 COLLECTION FORMS

Select the following commitment statements regarding study data collection forms:
HINT: Select ALL statements to confirm sponsor's agreement.

- **Data collection forms or electronic data capture (EDC) data input screens used by masked personnel will not include any identifiable treatment information (e.g., treatment, treatment code, treatment sequence).**
- **In cases where a previous data point may bias the observer, individual data collection forms and EDC data input screens will collect data for a single timepoint only (i.e., individual forms/screen will not collect data on the same animal(s) across multiple time points). In these cases, personnel will be trained not to refer to records from previous time points while collecting data.**

<If both boxes above are NOT checked:> **Explain why you did not check both boxes to confirm agreement with the statements above.** *<Click here to enter text.>*

Submit study data collection forms.

- ***Upload: UPLOAD a document containing all data collection forms to be used during the study. For data captured using an EDC system, include a single, blank screen shot (PDF format) of each data input screen as it appears to the data collector.***

  <Document upload is required.>

32.0 PROTOCOL

<Section 32.0 Protocol is only enabled if a protocol that is not "Blood Level Bioequivalence Study"/"Crossover (including RSABE analysis) or Parallel Design" is being submitted and user indicated accordingly in Section 1.0>

Upload: UPLOAD the protocol as a single Portable Document Format (.pdf) document. The single PDF should inly include the Protocol, associated SOPs, and data collection forms. The PDF file should meet the specifications as described in the CVM eSubmitter File Specification Quick Guide (link above).
<Document upload is not required.>

33.0 COMMENTS

Upload: If you have additional comments that you would like to include in this submission please UPLOAD a single PDF file that contains the information. The PDF file should meet the specifications as described in the CVM eSubmitter File Specification Quick Guide (link above).
<Document upload is not required.>