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Guidance for Industry

Active Controls in Studies to Demonstrate Effectiveness of a New Animal Drug for Use in Companion Animals

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Additional copies of this guidance document can be requested from the Policy and Regulations Staff (HFV-6), 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/AnimalVeterinary/default.htm or http://www.regulations.gov.

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance document advises industry on the use of active controls in studies intended to provide substantial evidence of effectiveness to support product approval for new animal drugs used in cats, dogs, and horses (i.e., companion animals). This guidance document is directed at clinical investigators who conduct studies using active controls and have a basic understanding of statistical principles. In this document, CVM compares studies that use active controls to studies that use either placebo concurrent controls or untreated concurrent controls. CVM uses these comparisons to illustrate the appropriate use of an active control.

In general, FDA's guidance documents 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. BASIC TERMINOLOGY AND DESCRIPTIONS

A. WHAT IS A PLACEBO OR UNTREATED CONCURRENT CONTROL?

A *placebo concurrent control* is an inactive preparation designed to resemble the new animal drug as far as possible (*see* 21 CFR 514.117(b)(4)(i)). An *untreated concurrent control* is the absence of any treatment (*see* 21 CFR 514.117(b)(4)(ii)). For the purposes of this document, placebo concurrent controls and untreated concurrent controls are referred to as placebo controls. In general, animals will be randomized to the investigational new animal drug or the placebo control.

B. WHAT IS AN ACTIVE CONTROL?

An *active treatment concurrent control* (active control) is a known effective therapy (*see* 21 CFR 514.117(b)(4)(iii)). The Center for Veterinary Medicine (CVM) recommends that the active control be a new animal drug approved for the same indications of the disease or condition in the

target species. A non-inferiority study measures the effectiveness of an investigational new animal drug by comparing it to an active control. In general, animals will be randomized to the investigational new animal drug or the active control.

C. WHAT IS THE TARGET POPULATION?

The *target population* refers to the animal population for which the new animal drug is intended. One example of a target population would be all horses of a class(es)/breed(s), size, weight range, sex, or age with the clinical disease or condition that the new animal drug is intended to treat.

D. HOW DOES THE CLINICAL STUDY RELATE TO THE TARGET POPULATION?

The applicant should enroll a representative sample of the target population. This process allows the applicant and CVM to make inferences from the results of the study to the overall target population, which is referred to as the inferential value of the study. Inferential value is considered in the context of all effectiveness study data, regardless of the type of control used.

E. WHAT IS A SUPERIORITY EVALUATION?

Studies with a placebo control as the comparison group use a superiority evaluation. An analysis for superiority uses measures of clinical improvement and statistical evidence from the study to determine whether the investigational new animal drug is superior to the control in the target population.

Under some circumstances, a study with an active control may also use this type of evaluation (see IV. D.).

In a study with an active control, if the investigational new animal drug is shown to be statistically and clinically superior to the active control, then the conclusion can be made that the investigational new animal drug is more effective than the active control. In this case the active control is treated like a placebo control.

F. WHAT IS A NON-INFERIORITY EVALUATION?

Most commonly the goal of studies using an active control is to show that the investigational new animal drug is non-inferior to the control. The conclusion of a non-inferiority analysis should be interpreted carefully. The only way to rule out absolutely any inferiority is to show superiority. The non-inferiority study seeks to overcome this dilemma by showing statistically that: a defined portion of the known effect of the active control is retained by the investigational new animal drug; and the difference between the investigational new animal drug and the active control is no worse than a predefined margin. The margin of difference is referred to symbolically as Δ.[1]

[1] Other sources may refer to the margin of difference or the non-inferiority margin as M.

G. WHAT IS THE MARGIN OF DIFFERENCE (Δ)?

The *margin of difference* or Δ, defines the extent to which the investigational new animal drug can be less effective than the active control and still allow the applicant and CVM to conclude that it is "non-inferior". The margin of difference is specified before conducting the study because it will determine whether a study supports the effectiveness of the investigational new animal drug. In the active control comparison, the results provide a point estimate of the difference between treatments and a confidence interval around that difference. In general, the study seeks to show that the upper bound of that confidence interval is less than the acceptable Delta (Δ).

H. HOW IS THE MARGIN OF DIFFERENCE DETERMINED FOR A NON-INFERIORITY STUDY?

The margin of difference (Δ) for a non-inferiority study is critically dependent on the effect size of the active control, which is known from previous placebo-controlled studies that evaluated the effectiveness of the active control. Reliance on a non-inferiority study assumes that the active control drug will have a similar effect in the non-inferiority study to the effect it had in the placebo control study that established its effectiveness. Because this is an assumption, the active control effect size estimate is generally chosen conservatively, e.g., as the lower bound of the two sided 95% confidence interval estimated from the success rate of the active control minus the success rate of the placebo from the placebo control study. The lower bound of the confidence interval becomes Delta$_1$ (Δ_1), the difference between the investigational new animal drug and the active control (AC-ID), that should not be exceeded, generally by showing that the 95 percent upper bound of the confidence interval for AC-ID is less than Δ_1. If this is shown, the study results will demonstrate that the investigational new animal drug has some effect (greater than 0) and that not all of the effect of the active control has been lost.

Basing the margin of difference only on Δ_1, i.e., showing that the effect is greater than zero and that not all of the effect of the active control has been lost, may not be sufficient to demonstrate non-inferiority. In addition, CVM may want assurance that a sufficient proportion of the effect of the active control is preserved. In general, the margin of difference should conserve 50 percent of the effect size, a value often called Delta$_2$ (Δ_2). For example, if a conservative estimate of the effect size of the active control versus the effect size of the placebo in the placebo-controlled study mentioned above was 20 percent, the margin of difference in the non-inferiority study would be no greater than 10 percent.

In cases where the active control was not tested against a placebo, an applicant could use information from historical evidence, such as scientific literature, expert opinion, and previous studies, to determine a clinically relevant margin of difference.

I. HOW IS A NON-INFERIORITY STUDY CONDUCTED?

In a non-inferiority study, one should calculate the difference between the success rate in animals treated with the active control and the success rate in animals treated with the investigational new animal drug (AC-ID), and calculate a two-sided 95 percent confidence interval for this difference. If the upper bound of this confidence interval (i.e., the degree of inferiority of the

new drug) is less than the margin of difference, then one can conclude statistically that the investigational new animal drug is non-inferior. For an example of a non-inferiority evaluation with a margin of difference, see Appendix 1.

J. WHAT FACTORS AFFECT STUDY SAMPLE SIZE?

Sample size in a non-inferiority study is determined by multiple factors, such as the estimated success rate of both the active control and the investigational new animal drug, the margin of difference, and the variance. For example, holding all other factors constant except the margin of difference, the smaller the margin of difference the larger the sample size, and vice versa. Also, if the estimated success rate of the investigational drug is less than the estimated success rate of the active control, the sample size would need to be larger than if the estimated success rate of the investigational new animal drug is greater than the estimated success rate of the active control (See Appendix 1).

III. GENERAL CONSIDERATIONS RELATED TO STUDIES USING AN ACTIVE CONTROL

Applicants should consider a number of issues when deciding to use a study with an active control or a placebo control. Some of the key issues are discussed here. Typically, placebo-control studies are preferable to non-inferiority studies in that they make fewer assumptions and can almost always have a smaller sample size.

A. ANIMAL WELFARE

The welfare of the animals enrolled in the study should be a major factor in determining whether to design the study with an active or a placebo control. In certain disease states or conditions, if an approved new animal drug is available, ethical considerations (mainly harm to the animal from getting no treatment) could predispose an applicant to design a non-inferiority study rather than a placebo-controlled study. The acceptability of a non-inferiority study versus a placebo-controlled study may vary depending on the disease or condition, the existence of approved new animal drugs that treat the disease or condition, the study design, and the patient population. For many studies, the protocol is reviewed by an Institutional Animal Care and Use Committee (IACUC) for evaluation of the welfare of the animal subjects.

B. OWNER ACCEPTABILITY AND COMPLIANCE

A non-inferiority study could have a higher enrollment and retention of client-owned animals compared with a placebo-controlled study. Animal owners could be more likely to enroll and less likely to remove their animals if they know their animals will receive treatment with an investigational new animal drug or an active control drug. Fewer dropouts facilitate the analysis and interpretation of the results; however, this potential benefit should be weighed against the disadvantages of a non-inferiority study.

C. CERTAIN DISEASES OR CONDITIONS FOR WHICH A PLACEBO CONTROL SHOULD BE USED

A placebo control should be used for those diseases or conditions that can be left untreated for a certain period of time. Applicants could design studies with an escape or rescue clause that switch all non-responders after a certain time point during the study either to the investigational new animal drug or standard of care if they had been assigned to the placebo group, or to standard of care if they had been assigned to the investigational new animal drug. The non-responders would be considered treatment failures.

D. DISEASES OR CONDITIONS THAT MAY IMPROVE SPONTANEOUSLY IN THE STUDY POPULATION

Some diseases or conditions have a high self-cure rate and improve without treatment. In studies involving such diseases or conditions, it will rarely be possible to determine a credible margin of difference (Delta, Δ) for the non-inferiority study (see Draft Guidance for Industry: Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval, Center for Drug Evaluation and Research (CDER), October 2007). In these instances, it will be necessary to use a placebo control instead of an active control.

IV. DESIGNING THE STUDY

A. WHAT CHARACTERISTICS SHOULD A DRUG HAVE TO SERVE AS AN ACTIVE CONTROL?

An active control should be an approved new animal drug in the target species for the same indication as the investigational new animal drug. For example, the active control in a study evaluating a new oncology drug should be effective against the same tumor type.

The active control's level of effectiveness was established at the time of its approval. The effectiveness should have been established, at least in part, from studies in which the drug was compared to a placebo control. In addition, for a drug to be an appropriate active control, the difference in effectiveness between that drug and its placebo control, is assumed to apply to the current study (the "constancy assumption"). Support for the constancy assumption is best provided by using as the active control a drug that was shown to be effective with placebo-controlled data. This approach should help support assay sensitivity (see B. below) and avoid a phenomenon known as bio-creep. *Bio-creep* refers to a sequential lowering of standards of effectiveness that happens when drugs are continually evaluated and approved using active controls in a sequence such as the following:

Step 1: Drug A is evaluated for effectiveness in a study with a placebo, and the conclusion is Drug A is superior to the placebo.

Step 2: Drug B is evaluated for effectiveness in a study with Drug A as the active control, and Drug B is considered non-inferior to Drug A, within the defined margin of difference.

Step 3: Drug C is evaluated for effectiveness in a study with Drug B as the active control, and Drug C is considered non-inferior to Drug B, within the defined margin of difference.

However, Drug C may be outside the non-inferiority margin that would have been established for a comparison with Drug A, resulting in a favorable statistical analysis for a drug that appears to be effective in the non-inferiority study when, in fact, it is not effective when used in the target population. It is thus critical that the choice of Δ_1 reflect actual data with the active control vs. placebo. If drug B were shown to be superior to drug A, there would not be a problem.

In special circumstances, a drug that has not been evaluated for effectiveness against a placebo could be selected as an active control. However, when this choice is made, both the applicant and CVM should evaluate the circumstances carefully and confirm the criteria for an evaluation of effectiveness are appropriate. The applicant should consider a superiority study comparing the investigational new animal drug to the active control (see IV. C.) or other modifications to the study design.

B. WHAT IS ASSAY SENSITIVITY?

Assay sensitivity is a study property defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment. Studies that lack assay sensitivity may conclude that an ineffective new animal drug is non-inferior to the active control because neither drug had any effect in the study, so that AC-ID is small. In this case, a small AC-ID is meaningless because neither drug would be found to be superior to placebo if a placebo group had been included in the study.

Assay sensitivity is determined from two sources: 1) historical evidence of effectiveness of the active control and 2) design of the proposed non-inferiority study. Historical evidence of effectiveness examines how the active control was originally determined to be effective. Preferably, effectiveness was determined by comparing the active control to a placebo control in a well-controlled study, making it likely that it would be superior to placebo in a non-inferiority study (although this superiority would not actually be measured). Identification of the smallest effect size that the active control can reliably be assumed to have is used to support the margin of difference. The proposed non-inferiority study design is appropriate when the historical estimate of the drug effect size is well supported by results of previous studies using the active control. The previous studies should conclude that the active control can consistently be distinguished from a placebo.

Using a study design similar to the design used to determine effectiveness of the active control enhances assay sensitivity, as discussed in the following section.

C. WHAT DESIGN CHARACTERISTICS SHOULD A STUDY WITH AN ACTIVE CONTROL HAVE?

The proposed study design for evaluating the effectiveness of the investigational new animal drug should be broadly similar to the study design originally used to evaluate the active control. Study design information may be obtained from published literature, Freedom of Information (FOI) Summaries, and labeling. In the absence of a placebo-controlled study for comparison, both CVM and the applicant should be confident the non-inferiority study will resemble the situation in which the active control was originally shown as effective as much as possible (the constancy assumption). Important similarities could include characteristics of the enrolled

animal subjects in the study, the severity of the condition or disease being treated, the use of similar response variables for measuring effectiveness, and similar concomitant therapy. CVM acknowledges that medical advancements in the treatment of disease conditions and changes in variables used to evaluate the effectiveness of the investigational new animal drug may result in necessary changes to a study design. Therefore, when there are important differences between the studies used to evaluate the effectiveness of the active control and the current proposed study, the applicant and CVM should discuss these differences in advance to ensure that the proposed non-inferiority study will result in a valid conclusion about the effectiveness of the investigational new animal drug.

The conduct of the non-inferiority study should mimic the conduct of the previous studies used to evaluate the active control as closely as possible. Any deviations could affect assay sensitivity. To ensure assay sensitivity, the study should actually enroll, treat, and evaluate patients in a manner similar to the studies used to support historical evidence of effectiveness.

D. WHAT TYPE OF ANALYSIS SHOULD BE USED WHEN THE ACTIVE CONTROL IS NOT AN APPROVED VETERINARY PRODUCT?

For those diseases or conditions for which the standard of care is a drug not approved by the CVM for the indication in the intended target species, an applicant should consider designing a study with the standard of care drug as the active control using a superiority analysis. However, its extralabel use must meet the requirements of 21 CFR § 530.30. The effectiveness study should demonstrate that the investigational new animal drug is clinically and statistically superior to the active control to be able to conclude effectiveness.

E. WHAT ARE SOME CHARACTERISTICS OF RESPONSE VARIABLES USED IN A NON-INFERIORITY EVALUATION?

As with any effectiveness study, an applicant should select clinically relevant response variables that are widely accepted as valid and having well understood characteristics. The measurement scale of each response variable should be sufficiently unbiased and reliable to provide meaningful distinctions between animals having different levels of the characteristic measured. These principles apply to all types of measurements, including dichotomous scales, such as "treatment success"/"treatment failure", "yes" / "no"; ordinal scales such as "normal" / "mildly affected" / "moderately affected" / "severely affected"; and variables that are continuously distributed, such as blood glucose or serum alkaline phosphatase. If more than one primary variable is used to assess effectiveness, each variable should support evidence of non-inferiority and clinical improvement. The criteria for assessing effectiveness should be determined in the protocol prior to initiating the study.

A non-inferiority study should use the response variables used in previous studies establishing the effectiveness of the active control because the historical experience used to support the non-inferiority margin is generally pertinent only to those variables.

However, if the applicant chooses to use variables in a non-inferiority evaluation that are different from the variables used in previous studies to evaluate the active control, the applicant

should use other sources, such as literature or other studies with a similar design, to support the choice of margin.

F. HOW SHOULD A STUDY WITH AN ACTIVE CONTROL BE DESIGNED?

Studies using active controls should use a parallel arm effectiveness study design. In a parallel arm study, animals are randomly assigned to treatment groups and receive either the investigational new animal drug or the active control. Study personnel, who are masked to the treatment assignment, evaluate the animals in the study. The study is generally carried out at multiple locations to support independent substantiation of evidence. In such cases, the applicant would usually design a randomization plan for each location. Generally, each location has approximately the same ratio of animals assigned to the investigational new animal drug and to the active control. However, the ratio does not have to be a 1:1 allocation between the investigational new animal drug and the active control. The sample size and allocation ratio should be based upon the initial estimates for effectiveness.

G. HOW MANY ANIMALS SHOULD BE ENROLLED IN A STUDY WITH AN ACTIVE CONTROL?

To estimate the appropriate sample size, the margin of difference, the estimated success rate for the investigational new animal drug, and the estimated success rate for the active control is determined. Sources of variability in the study are to be considered. These include, but are not limited to: variability of the response variables, variability among locations in a multi-location study, and variability within and among households or other grouping factors. It is difficult to make generalizations about the size of the studies for all types of drugs, diseases or conditions, types of animals, and settings. Statisticians use a variety of formulas and simulations to develop a recommendation for the number of animals that should be included in a non-inferiority study. Inferential value should also be considered when determining the number of animals to enroll in a study to provide meaningful conclusions and inferences to the target population from the results (see II.J.). In general, to achieve adequate statistical power, a study with an active control usually has more subjects in each group than a study with a placebo control.

For example, generally more subjects would be necessary if one or more of the following criteria are present:

- A high self-cure rate for the disease
- The margin of difference is small
- A lower cure rate for the investigational new animal drug compared to the active control (i.e., inferiority of the investigational new animal drug)

H. HOW DOES BIAS AFFECT A STUDY USING AN ACTIVE CONTROL?

In a non-inferiority study, investigators (and the animal owners) know that each animal in the study is receiving some form of treatment for the disease or condition evaluated (either with the investigational new animal drug or the active control). The study investigators and animal owners are masked to treatment group, however, the awareness that the animal is receiving either an active control or the investigational drug could lead them to put a positive interpretation on

their observations of an animal's condition. Investigators and/or owners could be more likely to score an animal enrolled in the study in the direction of "improvement" of the disease or condition than investigators and/or owners who are participating in a study with a placebo control. This bias could affect both treatment groups equally.

In a non-inferiority study, the response variables used to assess effectiveness should be based on the study that was conducted to approve the active control. If subjective variables were used to assess the effectiveness of the active control, we recommend you discuss with CVM whether objective variables now exist that can be used in place of those subjective variables. Non-inferiority studies that use subjective variables are more prone to investigator and/or owner bias than studies that use objective variables.

APPENDIX: EXAMPLE OF NON-INFERIORITY STUDIES

This section provides a basic introductory example of a non-inferiority study using a hypothetical study with an active control and investigational new animal drug with different outcomes. These examples are not intended to describe a full statistical analysis for a non-inferiority study but to provide an understanding of the process.

Here, the applicant plans to conduct a parallel arm study to evaluate the effectiveness of an investigational new animal drug, using an active control. Each animal is randomly assigned to one of two groups. One group receives the investigational new animal drug (ID), and the other group receives the active control (AC). At the end of the study, the applicant calculates the percentage of animals that are "cures" in each treatment group. This is the primary response variable.

Determining the margin of difference. For this example, the applicant and CVM have agreed on a margin of difference (Δ) of 0.15 (15%) for the non-inferiority evaluation. For a discussion on how to choose delta see Section II G & H.

Planning the non-inferiority evaluation. The study will be analyzed by calculating from the study data a two-sided 95% confidence interval for $\pi_{AC} - \pi_{ID}$.[2] The upper bound is determined by the following calculation[3]:

$$UCL = (p_{AC} - p_{ID}) + z_{(1-0.025)} \times \sqrt{\frac{p_{AC}(1-p_{AC})}{n_{AC}} + \frac{p_{ID}(1-p_{ID})}{n_{ID}}},$$

When the upper bound of the confidence interval is used, Δ is expressed as a positive value. If the upper bound of this confidence interval is less than 0.15 (or 15%) when the upper confidence level (UCL) is expressed as a percentage), then one can conclude statistically that the investigational new animal drug is non-inferior.

Evaluating the data. The five rows in Table 1 represent five different possible cases. ID_1 and ID_2 illustrate the situation in which the investigational new animal drug is slightly less effective than the active control but sample sizes are different. ID_3 and ID_4 illustrate the situation in which both the active control and the investigational new animal drug have effectiveness in the 90% plus range but the investigational new animal drug is less effective than the active control and there is an increased sample size. ID_5 illustrates the situation in which the investigational new

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[2] The symbol "π" represents the proportion of cures in the target population. π_{ID} is the proportion of cures with the investigational drug, and π_{AC} is the proportion of cures with the active control.

[3] The symbol "p" represents the proportion of cures in the observed study, p_{ID} is the proportion of cures with the investigational drug, and p_{AC} is the proportion of cures with the active control. n_{ID} is the number of animals that received the investigational drug, and n_{AC} is the number of animals that received the active control. $Z_{(1-0.025)}$ is the critical value of a standard normal distribution at 1-0.025. For simplicity, we assume the difference of proportions follows a normal distribution but this may not always be true. The formula with the square root sign is the estimated standard deviation used in the calculation of the confidence interval.

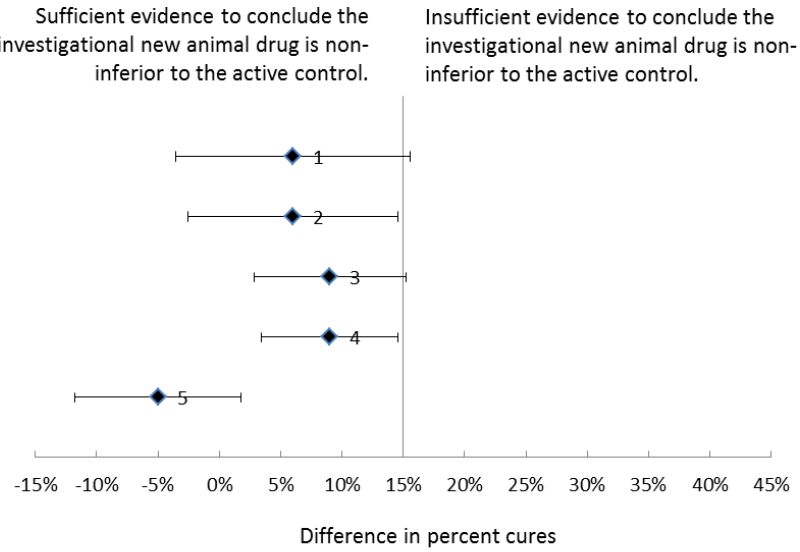
animal drug is more effective than the active control (though the study does not show superiority).

Table 1. Five hypothetical studies with an active control and a non-inferiority evaluation. The margin of difference, Δ, is 15%; randomization ratio is 1:1; significance level (alpha = 0.05). The table depicts the success rate proportions as percentages for ease of reading.

ID	N per group	p_{AC}	p_{ID}	$p_{AC} - p_{ID}$	Upper bound of the two-sided 95%confidence interval of the difference	Decision Outcome
ID_1	100	89.0%	83.0%	+6.0%	15.58%[1]	Insufficient evidence for a non-inferiority conclusion
ID_2	125	89.0%	83.0%	+6.0%	14.57%[2]	Non-inferior
ID_3	100	99.0%	90.0%	+9.0%	15.19%[1]	Insufficient evidence for a non-inferiority conclusion
ID_4	125	99.0%	90.0%	+9.0%	14.54%[2]	Non-inferior
ID_5	100	91.0%	96.0%	-5.0%	1.80%[2]	Non-inferior

ID – Investigational new animal drug
AC –Active control
p_{ID} – Percent cures of investigational new animal drug in study
p_{AC} – Percent cures of active control in study
$p_{AC} - p_{ID}$ – Difference in percent cures, active control - investigational new animal drug
[1]If the upper bound of the confidence (CI) of the difference is greater than 15% (margin of difference), the decision outcome is that there is insufficient evidence for a non-inferiority conclusion that the investigational new animal drug is non-inferior to the active control.
[2]If the upper bound of the confidence (CI) of the difference is less than or equal to 15% (margin of difference), the decision outcome is that the investigational new animal drug is non-inferior to the active control.

Figure 1. Five hypothetical non-inferiority scenarios with an active control. (Margin of difference = 15%; randomization = 1:1; alpha = 0.05)



If the right side of the horizontal line crosses the vertical line at 15% (defined margin of difference) there is insufficient evidence to conclude the investigational new animal drug is non-inferior to the active control.
If the right of the horizontal line does not cross the vertical line at 15% (defined margin of difference) there is sufficient evidence to conclude the investigational new animal drug is non-inferior to the active control.
Randomization ratio is 1:1; significance level (alpha = 0.05)

Figure 1 illustrates graphically the non-inferiority evaluation from the above cases. The figure depicts outcomes for the five investigational new animal drugs, ID_1-ID_5, presented in Table 1. The right end of the line depicts the upper confidence bound. To conclude that an investigational new animal drug is non-inferior to an active control, the upper bound of the confidence interval needs to be less than 15%.

Using Table 1 and Figure 1, CVM interprets the outcomes as follows:

ID_1: There is insufficient evidence to conclude that ID_1 is non-inferior to the active control. The percentage of cures was 83% with ID_1. The percentage of cures for ID_1 is numerically less than the percentage of cures for the active control (89%). The percent upper bound of the confidence interval of the difference between the active control and ID_1 is 15.58%, which is outside of our percent margin of difference (15%). CVM interprets this upper bound to mean that there is a reasonable chance that when ID_1 is applied to the target population, it might produce 15.58% fewer cures than the active control. This is not acceptable according to the agreed-upon criteria established at the protocol stage.

ID_2: CVM concludes that ID_2 is non-inferior to the active control. The percentage of cures for ID_2 and the active control are the same as for example one except that the sample size is increased to 125. The percent upper bound of the confidence interval of the difference between

the active control and ID_2 is 14.57%, which is just inside of our percent margin of difference (15%). CVM interprets this upper bound to mean there is a reasonable chance that when ID_2 is applied to the target population, it might produce 14.57% fewer cures than the active control. This is acceptable according to the agreed-upon criteria established at the protocol stage.

Notice that the study with ID_2 has more animals per group (125) than the study with ID_1 (100 per group). ID_2 is considered non-inferior even though the study resulted in a lower percentage of cures (83.0%) for the investigational new animal drug than for the active control (89.0%). The difference between ID_1 and ID_2 is the sample size. Thus, given the same study results, a larger number of animals will result in a narrower confidence interval and the conclusion can move from insufficient evidence for a non-inferiority conclusion to a non-inferior conclusion.

ID_3: There is insufficient evidence to conclude that ID_3 is non-inferior to the active control. The percentage of cures was 90.0% for ID_3 in this study. This is numerically less than the percentage of cures for the active control (99.0%). The percent upper bound of the confidence interval for the difference between the active control and the ID_3 is 15.19%, which is just outside of our percent margin of difference (15%). CVM interprets this upper bound to mean there is a reasonable chance that when ID_3 is applied to the target population, it might produce 15.19% fewer cures than the active control. This is not acceptable according to the agreed-upon criteria established at the protocol stage.

ID_4: CVM concludes that ID_4 is non-inferior to the active control. The percentage of cures for ID_4 and the active control are the same as for example three except that the sample size is increased to 125. The percent upper bound of the confidence interval of the difference between the active control and ID_2 is 14.54%, which is just inside of our percent margin of difference (15%). CVM interprets this upper bound to mean there is a reasonable chance that when ID_4 is applied to the target population, it might produce 14.54% fewer cures than the active control. This is acceptable according to the agreed-upon criteria established at the protocol stage.

Notice that the study with ID_4 has more animals per group (125) than the study with ID_3 (100 per group). ID_4 is considered non-inferior even though the study resulted in a lower percentage of cures (90.0%) for the investigational new animal drug than for the active control (99.0%). The difference between ID_3 and ID_4 is the sample size. Thus, given the same study results, a larger number of animals will result in a narrower confidence interval and the conclusion can move from insufficient evidence for a non-inferiority conclusion to a non-inferior conclusion.

ID_5: CVM concludes that ID_5 is non-inferior to the active control. The percentage of cures for ID_5 (96%) is larger than the percentage of course for the active control (91%). The percent upper bound of the confidence interval of the difference between the active control and ID_5 is 1.80%, which is inside of our percent margin of difference (15%). CVM interprets this upper bound to mean there is a reasonable chance that when ID_5 is applied to the target population, it might produce 1.80% fewer cures than the active control but this is acceptable according to the agreed-upon criteria established at the protocol stage. However, it does not demonstrate superiority to the active control because the upper bound of the confidence interval is above zero.

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