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Infectious Otitis Externa Drugs for Topical Use in Dogs

Guidance for Industry

Draft Guidance

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
March 2023

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance provides recommendations to help sponsors complete the effectiveness, target animal safety, and labeling technical sections of a new animal drug application (NADA) for infectious otitis externa drugs for topical use in dogs.

You may follow the guidance document or may choose alternate pathways for approval. We recommend that you discuss your proposed study plans with CVM, especially if you choose to use an alternative pathway for approval. We encourage you to schedule a pre-submission conference with CVM as you begin to make your investigational plans to ensure that you are completely informed about the requirements contained in the Federal Food, Drug, and Cosmetic Act and regulations.

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. Effectiveness

The effectiveness development plan for topical otic products should be designed to show that the drug product is effective for its intended use (i.e., to treat *otitis externa*) and, if it is a combination product, each active ingredient makes a contribution to the effectiveness of the combination. Effectiveness data in support of an approval for topically administered otic products include information to support dosage characterization and data to support substantial evidence of effectiveness. The recommendations regarding effectiveness data, including additional considerations for combination otic products, are discussed below.

A. Dosage Characterization

You should provide the scientific rationale supporting the dose, dosing interval, duration of treatment, and predicted duration of action for each component of a

combination drug and for the final formulation. You should also provide a scientific rationale for the volume per ear dose and whether animal size will be a factor in the delivery of the proposed volume into the ear canal. Dosing should be consistent with the mechanisms of action and local pharmacokinetics of the active ingredient(s). Dosage characterization is submitted under the Effectiveness technical section and a summary of the information provided will be included in the Freedom of Information (FOI) Summary.

There are multiple ways to support dosage characterization including, but not limited to:

1. Pilot Field Studies

Pilot field studies may help determine the appropriate dose, dosing interval, duration of treatment, and safety profile. Pilot field studies may also be conducted to determine which pathogenic microorganisms are responsive to the drug(s).

2. Published Scientific Literature

Published scientific literature, including individual or multiple sources, may be used to support a portion or all of the justification for the dosage and may significantly assist protocol development. For example, literature may provide information integral for the selection of optimal study time points or specify study design parameters for protocols for novel drugs and drugs with modified-release characteristics or extended duration of action. In general, sufficient scientific literature to reasonably support the basis for the dose characterization is acceptable; for example, a narrative review. Full scoping or systematic literature reviews are not routinely expected.[1]

3. Ear Wash/Swab Depletion Studies

CVM recommends that an ear wash/swab depletion study be conducted for all topical otic products to establish a final time of evaluation at which the ear can be evaluated for success or failure in the absence of effective drug concentrations. This may be used to determine the evaluation time (final evaluation day) to support substantial evidence of effectiveness. For topical otic formulations designed for a longer duration of activity, ear wash/swab depletion studies can be particularly helpful in estimating the duration of activity in the ear canal to justify the dosing interval, timing of evaluations, and the final evaluation day. The optimal use of ear wash/swab depletion data is during dosage characterization and dosing interval development to help identify a day or days when the drug levels are below the minimal inhibitory concentrations (MICs; for antimicrobials) or completely depleted (non-antimicrobials), so that the determination of success in the field study would be in the absence of drug. Without PK or *in vitro* data, the identification of the final evaluation

[1] See CVM GFI #106, "The Use of Published Literature in Support of New Animal Drug Approval" (https://www.fda.gov/media/70056/download).

day may be based on clinical response from a pilot study. The major limitation to choosing a final evaluation day based on clinical response in a pilot study is that the final evaluation could take place in the presence of therapeutic concentrations because the topical levels of drug are unknown. Evaluating the clinical endpoint in the presence of active drug is not appropriate because the infection could be suppressed, rather than cured, in the presence of the drug. Therefore, evaluation in the absence of drug better assesses the ability of the dosing regimen to treat the infection and decreases the potential for relapse.

The timing of the final evaluation day is dependent on the PK and the dosing interval of the active ingredient. For antimicrobials, the time of evaluation should be when the drug level is below the MIC90 for the pathogen of interest. Typically, the pathogen in the proposed indication that has the highest MIC90 is chosen as the worst-case scenario. The magnitude below the MIC90 that is chosen as a target, e.g., MIC90/2 or MIC90/4, is dependent on several factors, such as the drug's mechanism of action against the pathogen of interest, and should be supported by your data and/or published literature. In the absence of a well-characterized pharmacokinetic and pharmacodynamic target, as is generally the case for antifungals and steroids, the final evaluation should be conducted when the drug(s) is depleted (below the limit of quantification or LOQ).

Ear wash/swab depletion studies are conducted in healthy laboratory dogs or cats without otitis. Evaluating the kinetics of topical otic drugs in normal, healthy ears may not fully represent the depletion of the drug(s) in affected ears because the inflammation and disrupted skin barrier due to *otitis externa* could increase: 1) the systemic absorption of drug and 2) the rate of degradation, so that the depletion of the active ingredients may be more rapid in affected ears. Therefore, the ear wash/swab depletion study should only be used to help estimate the final evaluation day.

The dosing interval of the topical otic product should be considered when designing the ear wash/swab depletion study. For products that are to be administered once or twice daily, the sponsor should account for potential drug accumulation. For these products, you could either conduct a single dose study and perform a simulation to model the drug exposure after repeated doses, or administer repeated doses and then collect ear wash/swab samples after the last dose.

When designing an ear wash/swab depletion study, remember that each ear is NOT independent of each other and the animal should be considered the experimental unit, not the ear. Because of the potential high variability in the drug concentrations, you should sample up to, or past, the proposed final evaluation day, so that extrapolation is not needed to estimate duration of activity. Regression analyses used to model drug concentrations assume linear drug depletion, which may not always be the case. If you choose to use a regression analysis to extrapolate drug concentrations, you should use individual values (prediction intervals) rather than the mean values to maximize the inferential value from a small number of samples.

Ideally, you should conduct a pilot study to validate the study design and bioanalytical methods before performing the final study. Although there is no requirement that the final study or bioanalytical methods be carried out in compliance with FDA's good laboratory practices (GLP) regulations, if such studies are not conducted under GLP, CVM recommends that you identify any deviations from GLP and address the impact of these deviations on the data. In addition, CVM may request that you provide additional information, such as SOPs, to support the integrity of the data. Because of the lack of accepted methods for bridging topical formulations, you should use the final formulation in the ear wash/swab study. If a non-final formulation is used, you should identify any differences between the non-final and final formulations and address the impact of these differences on safety and effectiveness.

CVM recommends that you use a validated bioanalytical method to measure the free drug (active moiety) concentration of all the active ingredients. If the drug has multiple components, then the method should be able to differentiate these components.

B. Substantial Evidence of Effectiveness

1. Field Study

The purpose of the field study is to evaluate the safety and effectiveness of the drug in the target animal for the proposed indication(s) under the actual conditions of use. The field study should be multi-center (in geographically diverse regions within the USA), be randomized and double-blinded, be conducted in accordance with the principles of Good Clinical Practice (GCP), demonstrate safety and effectiveness, and use the final formulation.

The following are considerations for the design and conduct of the field effectiveness study:

a. Endpoint

Success criteria (i.e., clinical effectiveness) should be decided at the protocol stage. The protocol should numerically define a *success* via the scoring of clinical criteria (erythema, exudate, swelling, and ulceration) as evaluated by a veterinarian. The protocol should also include a clause that an animal cannot be classified as a success if an individual evaluation criterion received a higher score (worse score) on the final day as compared to the score at enrollment. The addition of this clause prevents an animal from being classified as a *success* if the ear actually worsened in one or more evaluation criteria during the conduct of the study. The minimum difference between enrollment and the definition of success should be large enough to reflect a clinical difference.

The sponsor should propose and justify the number of days after the last treatment

for the final evaluation of effectiveness. As discussed above, the final day of evaluation ideally should be determined by the ear wash/swab depletion study.

b. Treatment Groups

Studies supporting substantial evidence of effectiveness should be well-controlled, utilizing an appropriate control group. Refer to 21 CFR 514.117(b)(4) for more information about study design. The ratio of dogs receiving the investigational drug versus the control article should be considered in the design phase of the protocol.

The study should be masked appropriately to control for potential bias. The potential observable drug effects and routes of administration of the investigational drug and the control group should also be taken into consideration.

c. Inclusion/Exclusion Criteria

Field effectiveness protocols should specify inclusion and exclusion criteria. For example, to be included in the study each dog at enrollment should have a minimum clinical score as defined by the protocol and a confirmed bacterial and/or yeast infection based on an ear swab culture and identification by a microbiological laboratory.

Exclusion criteria should take into account concurrent disease, clinical course of otic disease (e.g., stenotic or calcified ears), use of concurrent medication, evidence of cranial nerve disease, and/or compliance of dog owners.

d. Patient Assessments

Methods and timing of ear examination, sample collection and analysis for cytology[2] and culture, bacterial/yeast identification, and ear cleaning procedures (and type of solution) should be standardized and clearly described in the protocol. If the protocol includes instructions to clean the dog's ears prior to administering the product, this condition of use should be included on the final product labeling in the "Dosing and Administration" section. Any ear cleaning solution used during the study should not have any antibacterial, antifungal, or anti-inflammatory component which would interfere with the effectiveness evaluation. In cases of bilateral *otitis externa* where both ears meet inclusion criteria, to decrease bias the protocol should specify whether the right or left ear will be evaluable in all such cases.

Clinical pathology (complete blood count, serum chemistry, and urinalysis) should be completed during the study to evaluate the effects of the product in the

[2] Ginel RJ, Lucena R, et al. A semiquantitative cytological evaluation of normal and pathological samples from the external ear canal of dogs and cats. Veterinary Dermatology. 13, 151-156 (2002).

target population. Hearing tests should be conducted by the investigator in all enrolled dogs at the beginning and the end of the study. If an aminoglycoside or other potentially ototoxic drug is used (as a test drug or an active control), the owner consent form should contain suitable language about possible deafness associated with products being used in the study.

e. Statistical Considerations

The study should enroll a sufficient number of subjects to adequately power the primary statistical test, taking into account subject attrition, censoring, and other factors that can affect the efficiency of the tests. The study should be powered to detect a clinically relevant effect size.

f. Microbiology

At the initial evaluation (Day 1), pre-treatment cultures should be collected for isolate identification to the species level (i.e., *Pseudomonas aeruginosa* and not *Pseudomonas* sp.). Sound scientific justification should be provided to include each organism as a pathogen in the final indication. β-hemolytic Group G streptococcus (i.e., *Streptococcus canis*) may be acceptable without further speciation if justified as a pathogen. CVM considers *Enterococcus faecalis* as a potential otic pathogen, but does not consider coagulase-negative staphylococci, *Bacillus* spp., or *Corynebacterium* spp as potential otic pathogens.

Treatment success indicates that the animal's *otitis externa* clinically resolved. Microbiological treatment outcomes are generally not measured because post-treatment cultures are generally not performed on animals classified at the final evaluation as a treatment success because normal flora exist in the ear and may provide conflicting data.

For antibacterial and antifungal products, susceptibility tests should be conducted in accordance with standardized methods described by the Clinical and Laboratory Standards Institute (CLSI), or by equivalent methods. Serial two-fold dilutions (usually centering on 1 µg/ml, e.g., 0.5, 1, 2 µg/ml) should be performed to determine minimum inhibitory concentrations (MICs). Measurements of quality control (QC) should be taken whenever possible. These should include well-characterized reference strains obtained from a recognized source (e.g., ATCC), for which MIC QC ranges are available. If no QC ranges exist for one of the antibacterial or antifungal drugs, a different representative from the same drug class for which QC ranges do exist should be tested to validate the testing method. CVM encourages the establishment of preliminary QC ranges for the drug through replicate testing (e.g., >30 tests). Favorable susceptibility test conditions for all pathogens proposed for the label should also be sought. Rarely will data only from disk diffusion susceptibility tests suffice. A separate antimicrobial susceptibility testing protocol may be submitted for evaluation or it may be submitted in conjunction with the field study protocol.

If you plan to pursue a product with two or more antimicrobials with overlapping spectra of activity, you should submit a justification for the inclusion of the additional antimicrobial(s). The submission should discuss the clinical importance of the target pathogen(s), the prevalence of the target pathogen(s), and address whether any one of antimicrobials could eradicate/control the infection alone. Following an appropriate initial justification, you should conduct a bactericidal study. The bactericidal study tests anticipated *in vivo* free-drug concentrations at the site of infection to determine if the additional antimicrobial(s) is needed to treat all of the target pathogens. For example, with a topical otic product containing gentamicin, the potential local *in vivo* exposure of free gentamicin may be ~1000 fold higher (assuming all drug is bioavailable) than the resistant *P. aeruginosa* clinical breakpoint. Thus, due to the local *in vivo* free-drug exposure likely being so high, gentamicin could kill the resistant *P. aeruginosa* alone and a second antimicrobial to target resistant *P. aeruginosa* would not be necessary.

g. Adverse Events

To accurately document adverse events, CVM recommends that the study include a log for the owner to complete while their animal is enrolled. This will provide information about time to resolution of symptoms and local adverse reactions.

h. Informed Consent

In addition to the general contents of an appropriate informed consent form, the consent form should contain suitable language about possible ototoxicity associated with the use of the investigational veterinary product(s) being used in the field study.

2. General Considerations for Combination Products

According to 21 CFR 514.4(c)(3), sponsors must "demonstrate by substantial evidence … that a combination new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling and that each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug."

For the purposes of this guidance, the requirements for a combination product are broken down into two elements.

Element 1 – A demonstration that the new animal drug combination is effective for all intended uses for which it is labeled.

For combination otic products, Element 1 is satisfied by the field safety study(ies) conducted in the target animal populations.

Element 2 – A demonstration that each individual active ingredient (AI) in the proposed new animal drug combination contributes to the effectiveness of the combination.

For combination otic products, Element 2 may be satisfied by either:

- a non-interference study conducted to demonstrate that each active ingredient contributes to the effectiveness of the combination product, or
- a written justification that may be based on literature, the known mechanisms of action, and/or the chemical properties of the components.

When considering Element 2, it is important to note that each AI or animal drug in a combination new animal drug is not required to contribute to the effectiveness of the combination in the same manner; and in some cases, a single study may be designed with the objective of demonstrating the contribution of more than one AI to the effectiveness of the combination new animal drug. CVM recommends that sponsors consider the contribution of each AI separately as they develop their plan to address the Effectiveness technical section.

a. Specific Recommendations for Combination Otic Products with Antimicrobial Components[3]

Studies of clinical isolates representative of the target pathogens in the proposed indication should be submitted to assess the susceptibility of the isolates to each active component and demonstrate non-interference between AIs. These *in vitro* studies should be designed with a factorial arrangement of treatment groups (a checkerboard design) to attempt to show that none of the AIs in the new animal drug combination interfere with the activity of any of the other antimicrobial AIs against their target pathogen(s). All AIs in the combination, including anti-inflammatory AIs, need to be included in such a study. For example, there are seven possible treatment groups for a three-way combination (A, B, AB, AC, BC, and ABC) plus the active and negative control groups.[4] These *in vitro* studies can also be used to satisfy Element 2 through their demonstration that each antimicrobial AI likely contributes to the effectiveness of the combination *in vivo*. The fractional inhibitory concentration indices (FICI) method is acceptable for characterizing such drug interactions. This method may be simplified if the final drug formulation ratio is known prior to initiating the FICI studies.

Whenever possible *in vitro* susceptibility and non-interference studies should follow CLSI standards or other appropriate validated standards, use appropriate QC strains, and, in general, use a two-fold dilution scheme. Dilution ranges for antimicrobials should encompass the MIC QC range of the QC strains. As

[3] We recommend that sponsors contact CVM regarding study design before conducting non-interference studies.

[4] Provided the ratio of the AIs to be used in the formulation of the final combination is known before starting the studies.

there are currently no CLSI standards for testing antifungal agents against *Malassezia pachydermatis*, CVM recommends using the broth dilution testing and QC guidelines described in CLSI's M27-A3 and M27-S3 for tests on this pathogen.

III. Target Animal Safety

Target animal safety (TAS) studies aim to identify the margin of safety and provide veterinarians with information regarding the safe use of the drug.[5] Safety studies conducted in the laboratory should be carried out in compliance with FDA's GLP regulations in 21 CFR part 58. This guidance includes recommendations specific for topical otic drug products.

A. Dosing

Both ears should be administered the full 1X, 3X, or 5X dose. In situations where it is not practical to administer the full 3X or 5X volume at one time due to ear capacity limitations, the dose may be divided and administered separately over a reasonable period of time (e.g., can be divided over 8 hours or a workday). CVM discourages dividing doses over multiple days. You should not manufacture a more concentrated product specifically for the 3X or 5X dose because it may alter the kinetics of the active ingredients. CVM recommends the study use the final formulation of the drug product.

If the product is intended to be massaged into the ear, the protocol should clearly describe the massage procedure (i.e., duration of massage and location of massage) after administration of the product to the ear. The protocol should state that the treatment administrator will minimize the ability of the animal to shake their head post-administration of the product to minimize any loss of the administered dose.

B. Duration and Frequency of Administration

Refer to Guidance for Industry (GFI) #185 (VICH GL43), section 2.4. *Dose, Frequency, and Duration of Administration*. You are encouraged to contact CVM prior to study conduct to discuss the specific drug and dosing schedule.

When proposing a duration and frequency of administration, you should provide a justification based on the active ingredient's known duration of action. For single dose products, you should propose an appropriate study duration and time period between redosing. CVM recommends the justification be based on PK data from your ear wash/swab depletion study, especially for long-acting products. The product should be administered frequently enough that the previous dose is not completely depleted in the ear, but not soon enough that the repeat dose artificially increases the chances of adverse events or harm to the animal. You should take into account long-acting products, excipients that improve absorption, and active ingredients that persist (e.g., terbinafine) in the ear when considering study duration and frequency of administration.

[5] See Guidance for Industry #185 (VICH GL43), "Target Animal Safety for Veterinary Pharmaceutical Products" (https://www.fda.gov/media/70438/download) for more details.

C. Control

CVM recommends a non-toxic placebo such as saline for solutions or mineral oil for suspensions.

D. Housing

Otic products tend to be lipophilic and can adhere to many surfaces for an extended period. Laboratory-held animals used in TAS studies can easily come into contact with investigational products if animals are comingled for socialization or other purposes. Therefore, the protocol should clearly address the commingling of animals in the treatment phase to ensure animals are unable to lick/ingest product from a neighboring animal. While commingling is acceptable during the acclimation phase, commingling during the treatment phase is discouraged.

E. Evaluation of Toxicity

The study should be designed to capture the drug effects at the time points of maximal exposure and/or maximal toxicity.

The method and frequency of aural, otoscopic, and hearing examinations should be specified in the protocol. The study should include pre- and post-treatment aural/otoscopic examinations and hearing tests pre-treatment and prior to necropsy.

Adrenocorticotropic hormone (ACTH) stimulation tests should be conducted for otic products containing corticosteroids. The minimal acceptable number of ACTH stimulation tests in a TAS study is two: one pre-treatment and one prior to necropsy. CVM recommends adding a third ACTH stimulation test at the point of maximum exposure (Cmax) after the first dose. The pharmacokinetic (PK) data may provide the point of maximum exposure for the corticosteroid component.

Necropsy procedures should include histopathology of the middle and inner ears.

IV. Human User Safety

Human user safety covers human exposures resulting from actual conditions of use and is part of the TAS technical section. Human user safety concerns should be addressed, including potential exposure to the drug and the active metabolites by veterinary personnel, people handling the drug, and people in contact with the animal. Informed consent for the field study(ies) is important to ensure that dog owners understand the risks of potential exposure to the drug and to the people and animals that may come in contact with the treated dog. Investigational and approved drug labeling should address human user safety concerns.

V. Labeling

The pathogenic species listed on the package insert will be determined by the results of the field effectiveness study that support substantial evidence of effectiveness. The inclusion/exclusion of a pathogen in the indication should be considered in consultation with a microbiologist. CVM lists the number of cases for each putative *otitis externa* pathogen species isolated in the field study in the FOI Summary to help explain why a particular species was not included in the indication. Generally, CVM includes all pathogens cultured during the field study in the FOI Summary.

The following Precaution statements are generally found on the package insert for a topical otic product. The Precaution statements may be changed and/or not included depending on the active ingredients included in the product (e.g., corticosteroid versus an NSAID).

Precautions

- The use of *[TRADENAME]* in dogs with perforated tympanic membranes has not been evaluated. The integrity of the tympanic membrane should be confirmed before administering this product. Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment.

- Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs.