

Appendix A. Executive Summary – Question Mapping and Analysis

I. Introduction

As stated in the Supporting Statement, the following knowledge gaps exist surrounding antiparasitic drug use and resistance: the current level of awareness and concern regarding antiparasitic drug use and antiparasitic drug resistance in US veterinarians and veterinary parasitologists; the commonly recommended and used strategies for detecting, monitoring, and/or managing antiparasitic drug resistance; and the knowledge of the types of information that would best assist end users in the safe and effective use of antiparasitic drugs. The Ruminant and Equine Antiparasitic Drug Use and Antiparasitic Resistance Survey is designed to elicit responses from US veterinarians and veterinary parasitologists regarding their concern about antiparasitic drug resistance issues, their experiences using antiparasitic drugs and combinations of existing antiparasitic drugs in clinical practice, their use of methods to detect and monitor antiparasitic drug use, and the management options they recommend to prevent or slow the development of antiparasitic drug resistance. This information will be used by the Center of Veterinary Medicine’s Office of New Animal Drug Evaluation to fulfill our mission to better communicate with our stakeholders and guide the development of best practices to expeditiously approve safe and effective antiparasitic drugs. Additionally, CVM hopes to gain insight into which types of information would assist end users in the sustainable use of antiparasitic drugs.

To that end, survey questions are designed to address the following questions:

1. What experience do individuals report regarding antiparasitic drug use and antiparasitic drug resistance?
 - 1.1. Is there current awareness of antiparasitic drug resistance in target animals?
 - 1.2. What target animal/drug/route of administration/parasite resistance relationships do individuals report?
 - 1.3. Which information sources do individuals use when determining which antiparasitic drugs to use or recommend?
 - 1.4. Do individuals recommend concurrent multiple antiparasitic drugs and/or rotation of antiparasitic drugs in individual or groups of animals?
2. Which strategies for detecting, monitoring, and/or managing antiparasitic drug resistance do respondents commonly use?
 - 2.1. Which methods do individuals use to detect parasites, determine if treatment is effective, or manage resistance?
 - 2.2. Is the choice of parasite control practices related to awareness or experience of antiparasitic drug resistance?
3. Which types of information would best assist end users in the safe and effective use of antiparasitic drugs?
 - 3.1. What additional types of information could FDA use that would best assist end users in the safe and effective use of antiparasitic drugs?
 - 3.2. Is there evidence that there is awareness of FDA’s current methods of disseminating information about indications and use of approved drug?

This document is designed to inform how FDA plans to use survey data to address the research questions.

II. Participant Characteristics:

Questions 1-10 provide respondent informed consent (Question 1) and respondent background information to be used to determine inclusion or exclusion and to form the basis for further comparisons of responses by credential (respondents with advanced parasitology degrees or respondents with DVM degrees only) (Question 2), employment and practice type (Questions 3 and 7), region (Questions 4, 5, and 6), and percent of practice, employment or research area devoted to animal species and classes that we are concerned about (Question 9). Individuals without US experience or who cannot report experience in equine or ruminant species (Question 8) will be excluded from the remainder of the survey and directed to the exclusion page. Practice type and percent of practice, employment or research devoted information gained from Questions 7 and 9 will be used to limit analysis for each class of animals to those who have $\geq 30\%$ of experience devoted to that target animal species/class. Respondents will be given a choice to repeat the Treatment Decisions and Detection and Management sections for another animal if they choose, but responses will only be considered for those who report $\geq 30\%$ of their focus area for that target animal species/class.

Respondents will be stratified by credential type (DVM's compared with those respondents with an additional MS/PhD in Veterinary Parasitology or MS/PhD in Veterinary Parasitology only). Predominant practice type will be compared with the percentage of area of expertise to validate responses and used to direct respondents to the appropriate target animal section of the survey. Analyses are contingent upon adequate sample observations for individual subgroups. In cases in which the numbers of observations per cell are too small for valid subgroup analysis, responses will be aggregated by major target animal type and reported accordingly. Additionally, the distribution of respondents by region and practice type will be compared to published distributions from the professional associations and the AVMA, as well as published information on major industry types per region. This will inform discussion of study coverage, response bias, and potential for the generalization of responses.

III. Survey Objectives

Survey Objective 1. What experience do individuals report regarding antiparasitic drug use and antiparasitic drug resistance?

It is important for the FDA to gauge the level of awareness of antiparasitic drug use in the field because if individuals are not aware of antiparasitic drug resistance that is occurring, they may be less judicious in their use of antiparasitic drugs, which in turn may accelerate the development of antiparasitic drug resistance. Also, the FDA is interested in learning if individuals will, in fact, report antiparasitic drug resistance. Non-reporting could be due to a lack of antiparasitic drug resistance occurring or a lack of monitoring for antiparasitic drug resistance. Subsequent questions will ask respondents about the types of diagnostic tools they are using to detect parasites and to monitor antiparasitic drug resistance. The FDA's interest is not in the actual numbers of antiparasitic drug resistance relationships reported, as this study is not designed to measure prevalence of antiparasitic drug resistance, but in whether or not different practice or credential types, or individuals performing certain diagnostic tests report different amounts and/or types of resistance or awareness of antiparasitic drug resistance. Also, individuals who are more aware of antiparasitic drug resistance may utilize different parasite control management

practices. Types of animal production, animal management, and parasite life-cycles differ regionally; therefore, it is important to include regional information in comparisons.

Survey Objective 1.1. Is there current awareness of antiparasitic drug resistance in target animals?

This question is addressed by responses to Questions 10 through 13, and Question 16. Question 10 asks respondents their level of awareness of the prevalence of antiparasitic drug resistance in eight classes of target animals: specifically if there is high, moderate, or low/no prevalence. To determine the classes, animals were separated by species, age groups (bovine and equine only), and industry type (bovine only). These separating criteria were decided by consulting CVM subject area experts and the published literature pertaining to antiparasitic drug resistance. To help decrease measurement error from reporting resistance in an animal class that a respondent may have no or little knowledge of antiparasitic drug resistance, respondents may also choose to indicate that they are unable to evaluate the level of resistance for each of the eight classes of target animals.

Question 11 asks respondents to characterize the level of risk for the development or expansion of antiparasitic drug resistance in the United States as high, moderate, or low for each of the same classes of target animals as in Question 10. Again, respondents will be able to note if they are unable to evaluate the risk for each individual class of target animals. Question 12 elicits whether or not respondents have experienced or witnessed what they consider to be antiparasitic drug resistance as defined in the survey in the US in horses, cattle, or small ruminants in the past three years. Respondents may indicate that they have, they have not, or that they are uncertain. Results will be stratified by regional information collected in Question 5 to account for regional differences in parasite epidemiology and climate in the US which may influence respondents' answers.

Question 13 allows respondents to report the target animal, antiparasitic drug used, route of administration and parasite for each antiparasitic drug resistance case that respondents have experienced or witnessed in the past three years. Analysis of this question will be primarily descriptive, i.e., reporting the percent for each animal class, drug, route, and parasite. Inferences about the actual amount of resistance that occurs with each of the variables will not be made given the possible lack of representativeness in the sample. This question will also be used as one measure of internal validity for the survey; respondents who report experience with antiparasitic drug resistance should be more likely to report being aware of antiparasitic drug resistance compared with those who do not report experience with antiparasitic drug resistance.

Question 16 addresses how involved respondents are in their clients' decisions regarding parasite treatment and control. Respondents whose clients involve them more frequently in antiparasitic drug use decisions may be more likely to report awareness of, risk of development, or experience of resistance, as reported in questions 10, 11, and 12.

We expect to report:

1. In those respondents reporting $\geq 30\%$ of focus area, the percent of respondents stratified by credential type (respondents with advanced parasitology degrees or respondents with DVM degrees only), reporting awareness of high, moderate, or low/ no prevalence of resistance and percent reporting high, moderate, or low risk of development or expansion of resistance in each target animal class.

2. In respondents with knowledge of antiparasitic drug resistance and experience in each class of target animals, the likelihood of veterinary parasitologists and veterinarians with degrees in parasitology to report awareness of the prevalence of antiparasitic drug resistance as compared to veterinarians without advanced parasitology degrees.
3. In respondents with knowledge of antiparasitic drug resistance and experience in each class of target animals, the likelihood of veterinary parasitologists and veterinarians with degrees in parasitology to report higher levels of risk of resistance as compared to veterinarians without advanced parasitology degrees.
4. In respondents with knowledge of antiparasitic drug resistance and experience in each class of target animals, the likelihood of veterinary parasitologists and veterinarians with degrees in parasitology to report experience or having witnessed antiparasitic drug resistance.
5. The percent of total reports for target animal class reporting an antiparasitic drug/parasite resistance relationship by antiparasitic drug used, route of administration, and parasite.
6. Percent of respondents reporting each proportion (<25%, 25% to <50%, 50% to <75%, or \geq 75%) of clients involving them in antiparasitic drug use decisions.
7. Likelihood of respondents reporting awareness of resistance (high or moderate compared with low/no resistance) by proportion of clients that involve them in antiparasitic drug use stratified by target animal classes (equine, bovine, and sheep and/or goats) in respondents with knowledge of the species and \geq 30% focus area of practice or employment devoted to the target animal class.

Survey Objective 1.2. What target animal/drug/route of administration/parasite resistance relationships do individuals report?

This question is directly addressed by question 13. As previously described, analysis of this question will be primarily descriptive, i.e., reporting the percent for each animal class, drug, route, and parasite. Inferences about the actual amount of resistance that occurs with each of the variables will not be made given the possible lack of representativeness in the sample.

We expect to report:

1. The percent of total reports grouped by target animal class reporting an antiparasitic drug/parasite resistance relationship by antiparasitic drug used, route of administration, and parasite. No hypothesis testing will be performed.

Survey Objective 1.3. Which information sources do individuals use when determining which antiparasitic drugs to use or recommend?

Question 17 directly addresses this research question. Respondents are asked to choose up to three methods that they use most often to determine which antiparasitic drug to use or recommend for an animal or group of animals of the target species (cattle, horses, small ruminants). This question offers multiple sources that individuals may use to gain information: veterinary continuing education conferences and peer-reviewed scientific journal articles, antiparasitic drug labels, marketing or promotional materials, empirical experience from previous experience with the drug or by testing the antiparasitic drug in the animal population, and personal recommendations from other veterinarians in a practice or institution.

Comparisons within subpopulations of survey respondents are the outcomes of interest. Potential differences in the sources of information or methods of determination used by respondents associated with characteristics such as credential (respondents with advanced parasitology degrees or respondents with DVM degrees only) or practice type would influence needs assessments, targeted educational campaigns, and other research areas.

We expect to report:

1. The percent of respondents who chose each of the seven answer choices stratified by target animal class in those respondents reporting $\geq 30\%$ of focus area devoted to that class. No hypothesis testing will be performed.

Survey Objective 1.4. Are multiple antiparasitic drugs used concurrently or sequentially in individual animals?

This question is informed by respondents' answers to questions 20, 21, and 22. Question 20 provides information regarding relative treatment frequency. The responses to Question 20 will be used for two purposes. First, to determine if responses are comparable to other published data and secondly, to serve as a benchmark to compare responses from Question 21 between respondents. Question 21 assesses whether or not individuals report recommending rotating antiparasitic drugs for routine deworming in cattle, either as a dichotomous outcome for cattle or by frequency in horses and small ruminants. Treatment regimens differ by age, therefore for Questions 21 and 22 respondents will be asked to indicate frequency in young animals and adult animals. In Question 22 respondents are asked whether or not they use or recommend the use of two or more antiparasitic drugs at the same time in individual animals. Respondents who report that they use two or more antiparasitic drugs at the same time will be asked which drugs they use together in cattle, horses, or small ruminants as determined by focus area of expertise or choice of target animal species/class in question 15. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, responses will be stratified by target animal class and categorized by credential type (respondents with advanced parasitology degrees or respondents with DVM degrees only) and dichotomous awareness (aware of moderate or high vs. aware of low/no antiparasitic drug resistance) or experience (report vs. does not report) of resistance. Statistical analysis will explore whether or not there is an association between use of multiple antiparasitic drugs concurrently or on a rotational basis in individual or groups of animals and credential type (respondents with advanced parasitology degrees or respondents with DVM degrees only) and awareness or experience of resistance. The most frequently used combinations will be reported, however no statistical analysis will be performed on this data.

We expect to report:

1. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the percent of respondents who recommend rotational deworming in young and adult cattle.
2. In those respondents reporting $\geq 30\%$ of focus area devoted horses or small ruminants, the percent of respondents who recommended each frequency of rotation in horses or small ruminants.

3. In those respondents reporting $\geq 30\%$ of focus area to the corresponding target animal class, the likelihood that respondents who report experience with antiparasitic drug resistance recommend rotating antiparasitic drugs compared to respondents who do not report experience with antiparasitic drug resistance, adjusted for region if warranted.
4. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the percent of respondents reporting concurrent use of multiple antiparasitic drugs in individual animals.
5. In those respondents reporting $\geq 30\%$ of focus area to the corresponding target animal class, the likelihood that respondents who report awareness of antiparasitic drug resistance recommend concurrent use of multiple antiparasitic drugs in individual animals compared to respondents who do not report awareness of antiparasitic drug resistance adjusted for region if warranted.
6. In those respondents reporting $\geq 30\%$ of focus area to the corresponding target animal class, the likelihood that respondents who report experience with antiparasitic drug resistance recommend concurrent use of multiple antiparasitic drugs in individual animals compared to respondents who do not report experience with antiparasitic drug resistance adjusted for region if warranted.
7. In those respondents reporting $\geq 30\%$ of focus area to the corresponding target animal class, the likelihood that respondents with degrees in veterinary parasitology recommend concurrent use of multiple antiparasitic drugs in individual animals compared to respondents without degrees in veterinary parasitology adjusted for region if warranted.
8. The types and frequency reported of antiparasitic drugs stratified by animal class.

Survey Objective 2. Which strategies for detecting, monitoring, and/or managing antiparasitic drug resistance do respondents commonly use?

Whether or not respondents report antiparasitic drug resistance may depend on whether or not they perform appropriate diagnostic tests to determine if use of antiparasitic drugs is effective in the animals that they are treating. Additionally, practices recommended and used by experts in the field of parasitology may differ from private practitioners. The next section elicits information about which diagnostic tools respondents are using. If individuals are not performing or recommending diagnostic tools appropriate for detecting and monitoring antiparasitic drug resistance, our hypothesis is that they would be less aware of and report less experience with antiparasitic drug resistance.

Survey Objective 2.1. Which methods do individuals use to detect parasites, determine if treatment is effective, or manage resistance?

This objective is addressed by survey questions 18, and 24 through 30. Question 18 asks respondents which of six methods for determining whether or not an antiparasitic drug is effective in cattle, horses, or small ruminants they use most often. The options are tailored to the animal class for the question and offer choices for empirical uses, diagnostic tests, and animal specific production data. Responses will be descriptively reported. Individuals who indicate that they perform or recommend fecal examination procedures in Question 23 will be asked which procedures they use, whether they use larval cultures to identify parasite species, whether they are familiar with and use the fecal egg count

reduction test (FECRT), the sampling method they use to determine sampling groups, the cut-off value for egg reduction used to determine the result of the FECRT, and, in the small ruminant section, whether or not they use other methods.

We expect to report:

1. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the percent of respondents choosing each method to determine whether or not an antiparasitic drug is effective in cattle, horses, or small ruminants stratified by animal class (bovine, equine, or small ruminant) and credentials (respondents with advanced parasitology degrees or respondents with DVM degrees only).
2. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the likelihood that the three most frequently used diagnostic methods are employed by respondents with advanced parasitology degrees compared to respondents without advanced parasitology degrees.
3. In those respondents reporting $\geq 30\%$ of focus area devoted to small ruminants, the frequency and likelihood that respondents reporting awareness or experience with resistance use larval cultures or other methods (for small ruminants) other than the FECRT to determine parasite species.
4. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, likelihood that individuals who report awareness or experience of antiparasitic drug resistance use or recommend the FECRT in cattle, horses, or small ruminants.
5. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the likelihood that respondents with advanced parasitology degrees use or recommend the FECRT compared to respondents who do not have advanced parasitology degrees in cattle, horses, or small ruminants.
6. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the association of the method of sampling and percent reduction calculation used in the FECRT and the credential type of the respondent (respondents with advanced parasitology degrees or respondents with DVM degrees only) and a respondent's report of awareness or experience with antiparasitic drug resistance in cattle, horses, or small ruminants.
7. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the likelihood that respondents with advanced parasitology degrees use or recommend a higher FECRT cutoff value to determine if treatment with an antiparasitic drug is successful in cattle, horses, or small ruminants.
8. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the likelihood that respondents who have experienced resistance or who reported moderate or high prevalence of antiparasitic drug resistance in the target animal class use a higher cutoff value than respondents who have not experienced resistance or did not report moderate or high prevalence.

Survey Objective 2.2. Is the choice of parasite control practices related to awareness or experience of antiparasitic drug resistance?

Management practices are important factors in the prevention or slowing of resistance. The FDA is interested in learning more about which practices respondents report most frequently and how the choice of practices recommended compares among subgroups. Question 31 suggests nine practices that have been suggested to be important in parasite control programs. Question 32 ascertains whether or not individuals have changed the management practices that they recommend in response to either information or experience with antiparasitic drug resistance to provide temporal information necessary for interpretation of Question 31. For example, if respondents report frequent resistance and are using or recommending the use of management practices considered appropriate to slow or prevent the development of resistance it is important to know if a change of management practices occurred due to the experience or becoming informed about antiparasitic drug resistance. In other words, were respondents using these practices when resistance developed, or are they now using these practices due to pre-existing resistance? This question also serves to examine response validity. Individuals who report that they have not changed management practices because they have not experienced any resistance should not have reported experience of resistance in Question 12.

We expect to report:

1. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the frequency of each management practice chosen for cattle, horses, and small ruminants stratified by credential type (respondents with advanced parasitology degrees or respondents with DVM degrees only) if a sufficient number of responses is received.
2. In those respondents reporting $\geq 30\%$ of focus area devoted to the corresponding target animal class, the likelihood that respondents with advanced degrees in parasitology or who report awareness of prevalence or experience with antiparasitic drug resistance in the corresponding animal class recommend each choice compared to respondents without advanced degrees in parasitology or who do not report awareness of prevalence or experience with antiparasitic drug resistance.
3. Frequency of respondents reporting that they changed management practices either as a result of experience with or information about antiparasitic drug resistance.

Survey Objective 3. Which types of information would best assist end users in the safe and effective use of antiparasitic drugs?

FDA is tasked with providing the information available to the public regarding the safety and efficacy of an approved drug through FOI Summaries and product labels. While no major decisions would be affected by responses from below, FDA would like to know which information is most useful to those who actually use the products and summaries. FDA is also eliciting opinions from veterinarians and experts on how combination antiparasitic drugs should be commercially available. FDA will consider opinions of respondents; however, approaches to the commercial availability of antiparasitic drugs will not be determined by these responses.

Survey objective 3.1. What additional types of information could FDA use that would best assist end users in the safe and effective use of antiparasitic drugs?

Product labeling is one way to provide information about the indications and use of an antiparasitic drug. Ratings offered in question 34 for the helpfulness of recommendations on how to detect antiparasitic drug resistance, warnings regarding antiparasitic drug resistance if warranted for a particular drug, and management recommendations to minimize the development of antiparasitic drug resistance will give the FDA further perspectives on the information that end users will find most useful.

Survey Objective 3.2. Is there evidence that there is awareness of FDA's current methods of disseminating information about indications and use of approved drug?

Question 35 asks respondents specifically about FDA's Freedom of Information Summaries that summarize the safety and effectiveness information used to support the approval of veterinary drugs. FDA is interested in whether or not there is any association between the awareness of FOI Summaries and the credential type of the respondent (respondents with advanced parasitology degrees or respondents with DVM degrees only) or the report of awareness or experience antiparasitic drug resistance.

We expect to report:

1. The likelihood that respondents who report awareness of prevalence or experience with antiparasitic drug resistance or have a degree in veterinary parasitology report that each of the three label options somewhat helpful or very helpful compared to respondents who do not report awareness of or experience with antiparasitic drug resistance or do not have a degree in veterinary parasitology.
2. For each target animals class, the frequency that respondents were aware of FOI Summaries by credential type (respondents with advanced parasitology degrees or respondents with DVM degrees only) and awareness or experience of resistance, stratified by animal class.

Questions 36, 37, and 38 allow respondents to offer opinions regarding issues surrounding FDA's regulation of antiparasitic drug products. While inferences regarding the opinions of all veterinarians are not possible given the current sampling methodology, it is important for FDA to allow stakeholder input into issues surrounding antiparasitic drugs and antiparasitic drug resistance. This information is exploratory in nature will be used only for non-binding, internal FDA considerations.