#106

The Use of Published Literature in Support of New Animal Drug Approvals

Guidance for Industry

This version of the guidance replaces the version made available in August 2000, which specifically addressed the use of a single article to support drug approval. This revision of the guidance document considers multiple uses of the scientific literature, including narrative reviews, systematic reviews, and meta-analysis to support approval of a new animal drug.

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2021-D-1155.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

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

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The Use of Published Literature in Support of New Animal Drug Approvals

Guidance for Industry

This guidance represents 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

The purpose of this document is to provide guidance to animal drug sponsors on specific areas of the approval process where the available scientific literature may be useful to support the approval of a new animal drug application (NADA), an abbreviated new animal drug application (ANADA), or a conditionally approved new animal drug application (CNADA), as well as methodologies to ensure the validity of conclusions drawn by animal drug sponsors from the scientific literature to support an approval.

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.

Definitions of key terms may be found in section V. *Glossary*. The Appendix to this guidance provides example tables for organizing published studies and the data they provide to assist with screening and eligibility for analysis and data extraction.

II. BACKGROUND

The original GFI #106 was published in 2000. Since its publication, animal drug sponsors have used literature to support various aspects of animal drug development and approval, including early stages of drug development, dosage characterization, microbial food safety, design of the target animal safety evaluation, prediction of potential adverse effects, and substantial evidence of effectiveness.

Animal drug sponsors have expressed interest in further leveraging information published in the scientific literature to support new animal drug approvals. Use of published scientific literature is of interest because it makes use of existing knowledge and may reduce the number of animals needed for studies to support approval, and in some cases may provide greater inferential value compared to individual studies conducted for the purpose of supporting an approval. Scientific literature may also be used to respond to specific regulatory questions, identify data gaps, and

inform protocol design.

However, use of scientific literature to support drug approval has its limitations. Although there may be a wealth of published data on a drug or drug class, underlying study protocols and original study data and records generally are not available, making it difficult to determine the quality of studies and confirm aspects of study conduct or design necessary to make a safety or effectiveness determination. Implementation of systematic methods to screen and analyze information across multiple publications may reduce the uncertainty resulting from analyzing limited information in individual studies.

III. CONSIDERATIONS FOR USING PUBLISHED LITERATURE

The Center for Veterinary Medicine (CVM) considers the quality of journals used in literature reviews when determining the validity of the review. CVM needs high-quality data to have confidence in its regulatory decisions.

Changes in the publishing industry have brought more opportunities to publish research and greater access to such research. Because of the vast number of research journals that publish on topics relevant to many aspects of new animal drug approvals, sponsors should consider the quality and integrity of sources of published literature. For published studies conducted outside the United States, sponsors should consider factors that could affect the generalizability of study results to the U.S. target population and conditions of use.[1]

New reporting guidelines, such as described by the REFLECT statement,[2] CONSORT,[3] STROBE,[4] and ARRIVE,[5] which are designed to improve the reporting of animal research studies, may increase the utility of such literature for regulatory purposes.

Some journals and scientific publications may be found in or as part of mainstream scientific databases. Certain journals may not scrutinize the studies and data they publish. CVM recommends consultation with subject matter experts to assess journal or publisher practices (e.g., robustness of the editorial or peer-review process and standards). Prior to submitting any published literature to support regulatory decisions, sponsors should confirm they have identified any retractions for literature included in their submission.

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[1] See CVM GFI #265, "Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs," (October 2021).

[2] REFLECT stands for Reporting guidElines For randomized controLled trials for livEstoCk and food safeTy. (https://meridian.cvm.iastate.edu/reflect/ - Accessed on March 2, 2023).

[3] CONSORT stands for Consolidated Standards Of Reporting Trials (http://www.consort-statement.org/ and as reported in https://www.bmj.com/content/355/bmj.i5239 - Accessed on March 13, 2023).

[4] STROBE stands for STrengthening the Reporting of OBservational studies in Epidemiology (https://www.strobe-statement.org/index.php?id=strobe-home - Accessed on March 2, 2023).

[5] ARRIVE stands for Animal Research: Reporting of In Vivo Experiments (https://www.nc3rs.org.uk/arrive-guidelines - Accessed on March 2, 2023)

A. Submission of a Single Published Study as the Only Supporting Documentation for a Safety, Effectiveness, or Product Quality[6] Decision

Studies to support new animal drug approvals are ordinarily conducted in accordance with Good Laboratory Practices (GLP) (21 CFR part 58) or Good Clinical Practices (GCP) (GFI #85 (VICH[7] GL9), "Good Clinical Practice"[8] (May 2001)). Sponsors are required to follow GLP regulations that establish requirements for non-clinical studies including safety and bioequivalence studies. Substantial evidence of effectiveness requirements consists of one or more adequate and well-controlled studies conducted in accordance with an appropriate standard of conduct (21 CFR 514.117). The standard of conduct generally used for effectiveness studies is GCP. Although GCP is a guidance rather than a regulation, studies conducted in accordance with the GCP guidance are more likely to meet requirements for substantial evidence.

While publications may describe a drug's safety, effectiveness, and chemical or pharmacological characteristics, most published studies are not designed or conducted to specifically address regulatory requirements for new animal drugs. Most studies published in the peer-reviewed literature aim to explore whether a drug or treatment may have an effect, and the discussion is often focused on the generation of hypotheses for further investigation. Studies conducted to support a new animal drug approval are required to demonstrate that the drug is effective, safe, and/or can be manufactured to meet quality standards. Further, guidelines for peer review and editorial decisions are not necessarily designed with regulatory review requirements in mind. An article that summarizes a single study may not contain sufficient details about the study plans, study conduct, quality assurance measures, clinical end-point descriptions, or methods of data analysis. All of these are needed to assess the reliability of the results and their applicability to the target animal population.

Generally missing from published literature are original study data and records, extensive documentation[9] of the study design, the study protocol, details of study conduct, data handling and storage information, and data analysis and interpretation. Where present, these additional details and documentation may allow a single published study to be considered adequate for making population-level inferences and ultimately a regulatory decision.

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[6] Section 512(d)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360b(d)(1)).

[7] "VICH" is the acronym for International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. The VICH is a trilateral program (United States, Japan, and the European Union) aimed at harmonizing the technical requirements for veterinary product registration.

[8] All FDA guidances for industry mentioned in this document are available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] Study documentation includes all records in any form (including documents, magnetic and optical records) describing methods and conduct of the study, factors affecting the study, and any actions taken. These records include, but are not limited to: protocol, raw data, reports, standard operating procedures, reference materials, and specimens.

Although information provided in a single published article may be insufficient, on its own, for CVM to make inferences and regulatory decisions, it may be used in a supportive fashion to fill critical data gaps. However, studies using inappropriate study animal populations, inclusion/exclusion criteria, dosages, routes of administration, design features (e.g., lack of masking or randomization, inappropriate statistical methods), or different formulations may not allow CVM to make any meaningful inferences.

If a single published study is intended to demonstrate safety or substantial evidence of effectiveness of a proposed new animal drug product, the following items, either included within the publication or included with the submission of a published study, will provide information on the value of the study. This is not intended to be an exhaustive list.

- The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relationship to study animal acquisition or randomization.
- Details on the masking procedures or impact on the study if masking was not performed.
- The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study.
- Randomization codes and documented study entry dates for the animals.
- Individual animal or herd source data for critical variables and pertinent baseline characteristics.
- Full accounting of all study animals, including identification of any animals with treatment data that have been omitted from analysis and the reasons for omissions.
- Complete information for all deaths and removals and details of any adverse event(s) regardless of whether the adverse event resulted in a death or removal.
- Documentation of the characterization of the test substance.
- Documentation of proper operating procedures and quality controls.
- Evidence that the study was conducted by investigators with properly documented training and expertise and a history of implementing such procedures effectively.
- Discussion of potential limitations and biases in the study in light of FDA requirements.
- Access to copies of the original recordings of observations.

B. Multiple Publications

There are several types of review methods that may be used to synthesize information from multiple publications (Grant and Booth 2009[10]). Review methods commonly used

[10] Grant, M. J., and A. Booth. 2009. "A typology of reviews: an analysis of 14 review types and associated methodologies." *Health Info Libr J* no. 26 (2):91-108. doi: 10.1111/j.1471-1842.2009.00848.x.

to support new animal drug approvals include narrative review, scoping review, systematic review, and meta-analysis. The choice of method(s) used depends on how the literature is intended to support the new animal drug application.

The literature review methods are presented below in an order of increasing levels of evidence. Evidence from systematic reviews of all relevant and appropriately designed studies are considered a higher level of evidence and are more likely to satisfy safety and/or effectiveness requirements than other literature review methods. However, other literature review methods are still integral to supporting portions of the new animal drug application, including identifying and/or filling gaps, and provide a foundation for the other methods.

1. Narrative Review

Narrative reviews are probably the most common type of reviews found in the scientific literature. They are often used to provide broad overviews, discussions, assessments of previous work, or to identify current knowledge gaps. Generally, they describe and evaluate a general question or range of topics. Sponsors often use narrative reviews for dosage characterization or to support some aspect of a protocol. They typically do not use or state the explicit processes used to compile, evaluate, synthesize, or report the evidence included in the review. They may not encompass all relevant published sources of evidence, and search strategies are generally not specified. These omissions limit the ability of others to reproduce the review independently. Sources of bias may be introduced into the review and may not be easily identified by the reader. Quantitative summaries (e.g., meta-analysis) of the body of evidence are typically absent.

For regulatory purposes, a narrative review should be comprehensive. Although not intended to be a systematic review (described in section III.B.3. *Regulatory Systematic Review* below), narrative reviews in new animal drug applications should incorporate some of the principles of a systematic review, such as transparency, balance, and limiting bias.

The scope of the literature search for a narrative review will depend on the topic or question(s) the sponsor is trying to address.

To improve the quality of the review, CVM recommends including information on the database(s) searched, the keywords or search string(s), and any limitations, such as date range(s) imposed. To ensure that bias was minimized, the sponsor should also provide the rationale for inclusion and exclusion of papers from the review discussion. Primary research articles are preferred, as review articles may introduce author bias.

In developing the narrative review, the following principles should be considered:

- Indicate the specific issues/questions the literature is intended to address.
- Discussion should be focused.

- Articles selected should be relevant to the current application (e.g., population, management practices, assay methods).
- Critically evaluate the available literature on the subject.
- Build the argument logically and present available evidence that both supports and refutes the desired position. It is important to include studies with unfavorable, as well as favorable results, and explain why unfavorable results may not be applicable or could be mitigated. The sponsor should draw conclusions based on their determination of what the literature supports.
- If there are major differences among studies, discuss possible reasons for disparate results.
- Identify where data gaps exist and recommend additional research that might help fill those gaps.

It may be helpful to group similar articles together and discuss whether or not a scientific consensus has formed around the topic, using the corroborating literature to support the thesis. If there are contradicting viewpoints or theories, supportive literature should be compared and contrasted to the common view and discussed critically. Some authors recommend structuring the literature review as an inverted triangle, by starting with the broad, overarching issue(s), then becoming more specific. Finally, the sponsor should draw overall conclusions and refer to the literature that supports such conclusions.

To expedite review, CVM recommends providing full copies of the papers used in the literature review (rather than abstracts) and a reference list. Complete and accurate English translations of foreign language papers used in the review must also be included (21 CFR 514.1(a)).

2. Scoping Review

A consensus definition of a scoping review is not currently available; however, for the purpose of this guidance, scoping reviews are defined as the process of systematically, but broadly and qualitatively, mapping the available literature on a topic, rather than answering a narrow research question. Because scoping reviews are high-level overviews and only qualitatively synthesize available evidence, they are not expected to be a labor-intensive or costly process. Scoping reviews should be used by sponsors when a repeatable and objective review of available evidence (both published and grey literature (see section V. *Glossary* for definition), and including proprietary reports available to a drug sponsor where appropriate) would improve the quality and efficiency of the drug development process, or allow a sponsor to evaluate the feasibility of a particular approach to generating the information necessary to satisfy the requirements of a technical section.

Sponsors should consider the use of scoping reviews in a variety of situations. For example, CVM generally recommends conducting a scoping review prior to the conduct and submission of a systematic review. A scoping review may allow a

sponsor to map available evidence related to the effectiveness of a new animal drug in an unbiased and qualitative manner to determine if a systematic review would be a feasible approach to demonstrate the substantial evidence of effectiveness. Potential topics to explore include dose, formulation, endpoints, conditions of clinical use, and inferential value for the target population. The results of the scoping review may also provide information necessary to develop the protocol for the systematic review, including the definition of appropriate inclusion or exclusion criteria, identification of reliable endpoints, and/or establishment of an appropriate control group. CVM anticipates that formal scoping reviews may also be useful to summarize pharmacologic and toxicologic properties of an active ingredient for use in the justification of target animal safety study designs (dose selection, overdose levels, treatment duration, and/or endpoints), or to justify innovative effectiveness study designs.

When a scoping review is desired, a protocol should be developed and followed. CVM encourages sponsors to discuss their scoping review plans and protocols before performing the review. The methods of the scoping review should be described in a protocol. A variety of published methods (Armstrong et al. 2011,[11] O'Brien et al. 2016,[12] and The Joanna Briggs Institute (Peters et al. 2020[13])) provide useful summaries of methods for developing a protocol for a scoping review. A scoping review should be performed in a way that minimizes bias for future systematic reviews and meta-analyses. Because of the importance of limiting bias, consider whether it is appropriate for those involved in the review to also participate in developing the protocol for the planned systematic review. Also, consider how concepts and presence or absence of certain inclusion criteria might impact objectivity of the reviewers. For example, if the scoping review is focused on concepts rather than results, objectivity may be maintained, so that the same group may work on both the scoping review and the protocol for the planned systematic review.

The scoping review protocol should include the following components:

a. Defined research question

The research question for a scoping review should be consistent with the objectives of the scoping review. The research question should include the population (e.g., species and class, if needed), the primary topic, and the context. Sub-questions may be necessary if the evidence needs to be divided by

[11] Armstrong, R., B. J. Hall, J. Doyle, and E. Waters. 2011. "Cochrane Update. 'Scoping the scope' of a cochrane review." *J Public Health (Oxf)* no. 33 (1):147-50. doi: 10.1093/pubmed/fdr015.

[12] O'Brien, K, D. Levac, A Tricco, W Zarin, E. Lillie, and S. Straus. *Current best practices for the conduct of scoping reviews.* Available at: http://www.equator-network.org/wp-content/uploads/2016/06/Gerstein-Library-scoping-reviews_May-12.pdf. University of Ontario 2016.

[13] Peters, M. D. J., C. Marnie, A. C. Tricco, D. Pollock, Z. Munn, L. Alexander, P. McInerney, C. M. Godfrey, and H. Khalil. 2020. "Updated methodological guidance for the conduct of scoping reviews." *JBI Evid Synth* no. 18 (10):2119-2126. doi: 10.11124/jbies-20-00167.

populations or there are multiple topics being evaluated. Unlike systematic reviews, research questions for scoping reviews do not restrict the evidence to certain dosages, single outcomes, or study types.

Examples of appropriate research questions include:

- What effectiveness outcomes are reported following the use of [drug or drug class] in [population of interest]?
- What formulations of [new animal drug/drug class] are reported for use [list of broad indications] in [species/class]?
- What comparative interventions (control group(s)) are reported in the evaluation of the effectiveness of [new animal drug/drug class]?
- What adverse effects are reported following the use of [drug or drug class] in [species or range of species]?

b. Literature search strategy

The search strategy including the terms and databases or other sources of information (proprietary reports, conference proceedings, etc.) should be clearly defined in the protocol. When searching a database, the search terms and strategy should be chosen with a consideration for the standard terms or dictionaries used for that database. The search terms and strategy should allow for sufficient breadth of coverage (published and unpublished, including proprietary research reports; reviews and primary research) while also balancing the feasibility of the review. Broad scoping review questions have the potential to lead to searches that yield a tremendous amount of literature, and limitations (e.g., language, date published) should be carefully considered to allow for a comprehensive, yet feasible review in terms of time and resources.

In order to refine search terms, an initial search of one database followed by a review of words in the title, abstract, and keywords may assist sponsors in the development of final search strategies for multiple databases. Revisions to the search terms and methods may be needed during the search process if additional keywords are identified or new sources are discovered. Protocol amendments that include a discussion of the changes and justification are expected.

The choice of databases should be clearly stated in the protocol and be made based on the review question with an aim of obtaining the most relevant literature.

The use of a librarian or other information specialist is recommended in the search term/strategy development and refinement. Reviewing the reference list of literature obtained in the initial search and/or contact with authors to request access to other publications may be appropriate depending on the topic, objective, and breadth of the literature. In some cases, these procedures are not feasible for scoping reviews and should be reserved for the systematic review.

c. Selection of studies

The protocol should describe the process and personnel (logistical details) used to select studies for inclusion in the scoping review. This process should result in study selection in a consistent manner that minimizes introduction of bias. At least two reviewers are recommended for screening the literature or other information sources. A process for comparing results and resolving disagreements should be described in the protocol for the scoping review. Consistency should be assessed after screening a limited number of publications and protocol amendments created as needed to simplify and/or clarify the screening and eligibility process and improve the consistency between reviewers.

A two-step process is recommended for efficiently selecting studies from which to extract information. In the screening phase, study titles, abstracts, and, in some cases, keywords are examined to eliminate irrelevant publications retrieved by the search. The protocol should state how results without abstracts should be screened as these reports have limited information on which to base screening decisions. The full text of publications that pass the screening phase should be reviewed during an eligibility phase to determine whether they meet the inclusion criteria; publications meeting inclusion criteria should have pre-specified information extracted, including data for potential inclusion in a meta-analysis if appropriate.

d. Extracting information from eligible studies

A detailed process for extracting data from eligible studies should be included in the scoping review protocol. At a minimum, the following data should be extracted from each publication or other reference: author(s), date of publication, country in which the study was conducted, objective(s) of the study, description of study population (numbers, species, class), methods, intervention, control comparator, outcomes, and a brief list of key findings. Similar to the study selection process, the protocol should specify that the review team will meet and discuss the data extraction process after the extraction from a limited number of studies to determine if revisions to the process are needed and to ensure all necessary data to address the review question(s) are extracted. Protocol amendments should be written as necessary.

e. Summarizing and reporting results

The protocol should describe how the results will be presented and described. Scoping reviews generally do not include a statistical analysis or a summary of quantitative safety or effectiveness results. In fact, such quantitative summaries are discouraged when scoping reviews are being used to develop the protocol for a systematic review because they are not supported by the broad objectives and associated methodology of the scoping review. However, a qualitative summary which addresses the objective(s) of the scoping review should be provided. The number of records identified, duplicates removed, number of

publications/references that met screening and/or eligibility criteria, and the final number of studies selected for data extraction should be included in the summary.

3. Regulatory Systematic Review (SR)[14]

The purpose of a regulatory systematic review is to answer a specific question or to reach a specific, evidence-based regulatory decision or recommendation. Systematic reviews aim to minimize bias by using explicit, systematic methods. In a regulatory systematic review, studies should be critically evaluated to ensure that they are relevant to the regulatory question and that the decision-making procedure or statistical analysis is appropriate for the intended purpose. In most systematic reviews used to inform healthcare decisions or make evidence-based recommendations, many publications/references may be eliminated, but the review may still be useful as supportive information. However, in a regulatory SR, eliminating many publications/references may lead to an inability to move forward with a regulatory decision or recommendation.

The results of a regulatory SR are specific to the particular animal drug product under consideration for the stated indication and condition(s) of use; conclusions cannot be transferred to another similar product or to a product from the same drug class.

a. Critical factors

Two issues that should be considered by sponsors early in the SR development process are the drug product formulation and the endpoints to establish safety or effectiveness, because they often affect the feasibility of using a regulatory SR approach to satisfy technical section[15] requirements for a new animal drug. These issues should be well-defined in the protocol.

i. New animal drug product formulation

The formulation includes the active drug ingredient as well as the inactive ingredients. The SR should evaluate the formulation of the new animal drug for which approval is sought and which is produced in accordance with appropriate manufacturing practices (i.e., final formulation). The final formulation and any acceptable deviations from the final formulation should be defined in the protocol. Depending on the purpose of the SR (e.g., effectiveness, target animal safety), the decision to include or exclude an individual study based on the formulation may differ, as other formulations may also include information useful for safety evaluations (e.g., differences in exposure). Formulation should be taken into consideration in the selection of

[14] For the purposes of this guidance, the term "systematic review" is used synonymously with "regulatory systematic review."

[15] Information to support the approval of an NADA are contained in seven technical sections: Effectiveness, Target Animal Safety, Human Food Safety, CMC, Environmental Impact, Labeling, and All Other Information. See GFI #132, "Administrative Applications and the Phased Review Process," (May 2018).

studies that are appropriate for inclusion. All individual studies included in the SR should have sufficient detail to confirm the identity of the drug included in the study for comparison to the new animal drug.

Literature using the proposed final formulation manufactured by or for the sponsor provides the best, most relevant evaluation and the highest evidentiary weight. Unless appropriate justification is provided, literature that does not use the final formulation of the proposed new animal drug product provides less weight in the evidentiary support scheme. Formulation changes to a drug product may occur over time and will be evaluated on a case-by-case basis to determine their significance. Such formulation changes may alter the identity, strength, quality, purity, or potency of the drug. If there are differences in the formulations of the drug(s) reported in the published literature and the proposed new animal drug product, the sponsor should carefully evaluate the formulation differences and the impact of those differences on the safety or effectiveness evaluation. Sponsors should justify how information from references that do not use the proposed final formulation supports the approval of the specific proposed product. References that are not relevant to the evaluation should be eliminated. If a sufficient number of studies using an acceptable formulation are not available and/or a connection to information found in the Chemistry, Manufacturing, and Controls (CMC) technical section cannot be made, the SR approach may not be appropriate.

ii. Choose appropriate endpoints

As discussed above, studies should be critically evaluated to ensure that they are relevant to the regulatory question. SRs should assess the scientific outcome(s) associated with the use of the drug, whether negative or positive. Sponsors should consider whether there are a sufficient number of studies that report the appropriate finding(s) in a consistent manner so as to allow for an evaluation of the safety or effectiveness of the new animal drug product. A scoping review, as described in section III.B.2. *Scoping Review*, may be instrumental in selecting endpoints of interest supported by the literature as well as determining whether a sufficient number of studies are available to support safety or effectiveness.

b. Development of a protocol for an SR

Before conducting an SR, sponsors should define an appropriate review question and write a protocol. In many cases, a scoping review of relevant literature will also assist in the development of the protocol. Sponsors should consider the resources necessary to conduct an SR, including the need for an information specialist, software programs to document the study selection process and to carry out the SR, and the time necessary for the review team to implement the SR process.

i. Developing the review question:

Various sources[16,17,18] describe SRs as a means to collate all evidence that fits pre-specified eligibility criteria in order to address a specific question. An organized and well-conducted systematic review begins with the formulation of a focused problem or question. The problem or question states the objective of the review. The question usually takes the form of Population + Intervention (or Exposure) + Control + Outcome (PI(E)CO). The WHO Handbook[19] describes the key components and provides examples of a well-formulated question for SRs. Although most of these sources are focused on questions related to human medicine, many elements are equally applicable to veterinary medicine. In addition to the general framework for question formulation, regulatory SRs should be designed to answer a specific regulatory question.

Following the PI(E)CO format, a "review question" for a regulatory systematic review will usually include the following components: the study animal population/intended species and class (P); the new animal drug product and in some cases the specific indication (I); the type of control, such as untreated concurrent controls and/or active concurrent controls (C); and endpoints (outcome measures) (O). For example, the review question for an SR to demonstrate effectiveness of a new animal drug may be described as follows: *To evaluate the effectiveness of [new animal drug product name] for [specific indication] as compared to [control group identification] in [animal species/class] based on [endpoint/outcome measures]*.

ii. Scope of relevant literature:

Once the review question has been formulated, and before developing the protocol for the SR, the sponsor should perform a scoping review of available literature for the purpose of developing the review question and/or evaluating the feasibility of a regulatory SR (see section III.B.2. *Scoping Review*).

Many factors influence the number of studies that may be included in the regulatory SR to address the question of interest (e.g., intended population,

[16] Centre for Reviews and Dissemination. Systematic Reviews CRD's guidance for undertaking reviews in health care (2009). Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf - Accessed on March 2, 2023.

[17] European Food Safety Authority. Guidance of EFSA: Application of systematic review methodology to food and feed safety assessments to support decision making (2010). Available at: https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2010.1637 - Accessed on March 2, 2023.

[18] P. T. Higgins et.al. Cochrane Collaboration (2011). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated February 2021). Available at: https://training.cochrane.org/handbook - Accessed on March 2, 2023.

[19] WHO Handbook for Guideline Development Geneva, World Health Organization. Available at: https://www.who.int/publications/i/item/9789241548960 - Accessed on March 2, 2023.

breadth of indication, quality of studies, assessment of bias of studies, the inferential value of the available studies, and independent substantiation across the studies). Although there is no standard or minimum number of studies which should be included, the number of studies should be sufficient to support a regulatory decision commensurate with the regulatory standards currently in place for prospective studies. If a meta-analysis is proposed, the number of studies included should provide adequate statistical power.

iii. Writing the protocol:

All regulatory SRs should be conducted in accordance with a protocol.

Protocol review by CVM is not required, but it is strongly recommended for any study intended to support an application. Protocol concurrence helps to prevent expenditure of resources on a study that CVM is less likely to accept. Sponsors are encouraged to discuss specific questions about protocol design in early communications with CVM's Office of New Animal Drug Evaluation (ONADE).

At a minimum, the protocol should include the following components:

- Study objective:

  The protocol should include a clear statement of the study objectives (e.g., the objective of the study will be to evaluate the effectiveness of a specific formulation of drug, given at a defined dosage, for specific indications (and conditions of use) in specific species/classes). The objectives of the study are generally synonymous with the review question.

- Standard of conduct for SRs:

  The SR should be conducted in accordance with an appropriate standard of conduct. Systematic reviews are, by nature, retrospective, and do not meet the definition of either a clinical study or nonclinical laboratory study. Elements of standards of conduct that apply to systematic reviews include: protocol development; organizational structure to ensure appropriate control of the study (e.g., investigator responsibilities, oversight (monitoring), quality assurance, quality control, and qualifications of personnel); procedures to ensure appropriate study documentation and archiving; and the documentation of the study conduct and results in a final study report. Standard expectations for data quality 9attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)) and integrity (credible, consistent, corroborative (CCC)) apply.

- Control type:

The systematic review protocol should include a design which permits a valid comparison to an appropriate control group and should evaluate the drug in the appropriate study population (species/class(es)). It should use methods to minimize bias on the part of observers and analysts of the data that are adequate to prevent undue influences on the results and interpretation of the study data. The systematic review should include procedures to identify, evaluate, and minimize bias both within an individual study and across the studies included in the systematic review.

The type of control chosen should appropriately reflect the review question and endpoints of interest and should adequately characterize the effect and variability in outcome in the population of interest in the absence of the new animal drug. Generally speaking, there are four types of control groups: untreated concurrent control, placebo control, active controls, or historical controls (21 CFR 514.117(b)(4) and the 2015 Joanna Briggs Institute Reviewer's Manual).

In general, the most suitable control group data source is one that can be generated from the eligible studies included in the SR that also had treatment groups included in the meta-analysis (concurrent control). However, even if the studies selected for the SR are randomized/controlled studies, there may not be a sufficient number of included studies with the selected control group (negative control vs. active, etc.). In many cases, a mixture of study designs may be available for potential inclusion in the SR, including, in some cases, studies which do not have a concurrent control group. Studies that do not have the control group of interest should not be automatically excluded from the SR. In situations where not all eligible studies include the control group of interest, mathematical procedures may be employed to adjust the estimated control group effect size to account for unknown extraneous influences (Hunter, Jensen, and Rodgers 2014).[20]

If a control group cannot be compiled from the studies that also had treatment groups included in the meta-analysis, use of a historical control group may be appropriate for the regulatory decision in certain situations (e.g., studies in which the effect of the new animal drug is self-evident or studies of diseases with high and predictable mortality, or signs and symptoms of predictable duration or severity, or, in the case of prophylaxis, predictable morbidity) (see 21 CFR 514.117(b)(4)(iv)).

- Literature search strategy:

  A literature search strategy should be described which has a high likelihood that articles relevant to the review question will be retrieved.

[20] Hunter, J.E., J.L. Jensen, and R. Rodgers. 2014. "The control group and meta-analysis." *Journal of Methods and Measurements in the Social Sciences* no. 5 (1):3-21.

The protocol should include a description of the databases, search terms (keywords and Boolean operators), date and language restrictions, plans for hand-searching of certain publications (e.g., review articles) or personal contact of scientists, and a search of other sources of information such as conference proceedings, unpublished studies, theses, or dissertations.

Sponsors should include relevant pilot work or otherwise non-publicly available, proprietary studies in the regulatory SR. By not restricting the studies to those that are published, publication bias may be reduced.

The methodology of indexing within a database (e.g., the use of controlled vocabulary) should be considered in the design of the search strategy. As with scoping reviews, the inclusion of an information specialist in the design and implementation of the literature search is recommended. Overall, the description should be sufficient to allow the search to be repeated with the same results.

- Study selection (screening and eligibility assessment):

A highly sensitive literature search may retrieve many studies which are not relevant to the SR. Therefore, the protocol should describe methods for choosing the studies including first screening the full list of literature (based on title, abstract, and keywords) and then reviewing full reports to determine the eligibility for inclusion in the SR. Appropriately designed screening inclusion and exclusion criteria are important for identifying literature that will contribute to a comprehensive database in an efficient manner without excluding relevant literature. The criteria should ensure the selection of studies which are designed to answer the review question for the particular drug formulation for the indication and conditions of use. The protocol should describe the use of more than one reviewer for conducting the screening and eligibility assessments to minimize the risk of error and/or bias. In addition, the protocol should describe the process for resolving disagreements between reviewers, if they occur (e.g., use of a third independent reviewer). The final study report should describe the numbers of reports that were screened, as well as the number that passed screening and eligibility phases and were ultimately included in the qualitative or quantitative (meta-analysis) assessment.

Examples of screening criteria:

Type of study: The types of studies utilized for the review will depend on the objectives of the study. Examples include prospective randomized studies, cluster randomized control trials (RCTs), some types of non-randomized controlled studies, cohort studies, and case control studies. Review articles are generally excluded but are used for hand-searching of additional references.

Study animals: The studies are usually limited to the species (and class if necessary) for which the new animal drug is intended.

Treatment: In the screening phase, criteria are usually specific only to the active ingredient because the title, abstract, and/or key words do not always provide enough information to identify specific drug products. At this phase, citations that are specific to alternate dosage forms or formulations which would not be used in the SR are excluded.

Outcome measure: Whether or not a study includes a particular outcome measure is not always evident from the title, abstract, or keywords. Broad criteria are necessary to avoid excluding relevant studies. For example, if the outcome of interest is specific to a disease, it would be appropriate to include citations for studies in which a drug is used for the treatment of that disease. The evaluation of the full text of the study report may be necessary to determine if the outcomes of interest were used in the study.

For those citations with insufficient information to enable a screening evaluation using the inclusion/exclusion criteria, the protocol should allow for an evaluation of the full report in the eligibility phase of the study. For example, some citations (particularly those in foreign languages and/or without abstracts) do not have a sufficiently detailed title to allow for an appropriate screening assessment. If, after reviewing the full text, the reviewer determines that the report does not meet the screening criteria, it should be included in the counts of reports that did not pass the screening phase of the SR.

Generally, the eligibility criteria build upon screening criteria and require more specific information that is found in the full text of the study report.

Examples of eligibility inclusion/exclusion criteria:

Treatment: For many SRs, eligible studies include a specific drug product (including the intended formulation). Criteria should be established to allow for confirmation of formulation and other information as needed and consistent with the purpose of the SR.

Animal information: If certain animal characteristics (e.g., disease state) are critical to the objectives of the study, these should be defined in the eligibility criteria.

Outcome measure(s): Outcome measures should be defined with the specificity necessary for the objectives of the study. Typically, these outcome measures are described with the same level of detail as required for a prospective study to demonstrate the safety or

effectiveness of the new animal drug.

Confounding factors: If certain confounding factors would invalidate the interpretation of the study in accordance with the review question, these should be described in the eligibility criteria. For example, if the SR is designed to evaluate the effectiveness of an antiparasitic drug against a certain parasite, the administration of an additional concurrent antiparasitic drug with known activity against that parasite in a study would not allow the inclusion of that study in the SR.

- Data extraction plan:

  The protocol should describe the methods for data extraction from studies that meet the screening and eligibility criteria. The data extracted from the study should include qualitative and/or quantitative information (depending on the objectives of the SR), information related to the screening and eligibility determination, characteristics that relate to the quality of the study, and data necessary for the synthesis and analysis of the data (if applicable).

  Examples of the information that may be extracted from each study include, but are not limited to: authors, year of publication, study animal identifying information (class, breed, age, physiological condition, etc.), case definition, location of study, identification of treatment or control arm, number of animals treated, number of animals used in the statistical analysis, product specific information (formulation, dose, route of administration, etc.), endpoint identification, use of a concurrent control group, experimental unit, randomization information, use of masking, quality standard to which the study was conducted (GCP, GLP, unknown), identification of any quality assurance or monitoring procedures, qualifications of study personnel, availability of raw data, how endpoint variability is reported (error mean square, standard error of the mean, etc.), and identification of any field safety assessments (e.g., clinical exams, clinical pathology, necropsy, and/or histopathology). Contact with authors or access to raw data may be helpful in addressing gaps in data availability or quality assessment that exist in the publications (e.g., for verification of masking, exclusion of publications due to lack of information, connecting the formulation in the publication to the formulation to be evaluated in the CMC technical section).

  The extracted data should be entered into an appropriate database which can be used for quantitative or qualitative evaluation.

- Study quality assessment

  The protocol should describe the assessment criteria for individual studies in order to identify study limitations such as lack of allocation

concealment, lack of masking, completeness of data, and incomplete or selective accounting of outcomes. The criteria and methods for the assessment should be defined in the protocol to ensure consistent application for each study.

The protocol should select the most likely types of bias to evaluate based on the types of studies (e.g., RCTs, observational).[21] At a minimum, the protocol should describe the assessment of bias in individual studies; define the criteria for the determination that the risk of bias is "high," "low," or "uncertain" for each bias type; and state that the support for the assessment will be documented as part of the data extraction process.

The protocol should state how the SR will be assessed for the overall quality of evidence, including, but not limited to, assessment of individual study limitations, research group bias (e.g., if the bulk of data comes from one group and how that is weighted), reporting biases (e.g., publication bias, time lag bias, location bias, citation bias, language bias, outcome reporting bias), magnitude of effect, dose response, precision of estimates, consistency of results, and directness of evidence.

- Statistical analysis methodology:

  The protocol for each study should describe the plan for the qualitative or quantitative assessment, depending on the objectives of the study, including any statistical analysis or risk assessment approach. If the intent of the SR is to conduct a meta-analysis, the protocol should include appropriate methods for statistical analysis and assessment of bias which are adequate to assess the effects of the new animal drug. For additional information on meta-analysis, see section III.B.4. *Meta-analysis* below.

- Results presentation:

  The protocol should describe the methods that will be used to present the findings of the study (forest plots, summary of findings tables, etc.). In addition to the findings presented, complete references including complete and accurate English translations of foreign language references must be provided (21 CFR 514.1(a)) and any raw data available for the studies included in the assessment should be provided.

- Basis of study conclusion:

  The protocol should describe the methods that will be used to evaluate the quality of the evidence and interpretation of the results of any statistical analyses. The discussion should identify remaining gaps and characterize

[21] "Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors." Available at: https://epoc.cochrane.org/resources/epoc-resources-review-authors - Accessed on March 2, 2023.

any limitations to the conclusions that may be drawn from the literature or caveats which exist. Sponsors should formulate proposals addressing any gaps by means of a field study, protocol-controlled retrospective study, or other acceptable method.

4. Meta-analysis

Depending on the objective and endpoints of the systematic review, CVM may recommend a meta-analysis within an SR. The term *meta-analysis*, as used in this document, refers to the combining of evidence from relevant studies using appropriate statistical methods to allow inference to be made to the population of interest.[22] Results from the meta-analysis provide a more general estimate of the effect than those derived from individual studies. A meta-analysis includes an estimate of effect size (the strength or the magnitude of the effect of an independent variable [treatment] on a dependent variable [outcome] in an experiment) and an evaluation of statistical significance of effect size (this includes an evaluation of variation of effect size between and within studies, and an assessment of bias).

Subject level data is not required to conduct a meta-analysis. A meta-analysis may be conducted with data aggregated to the level of each treatment group, combined treatment groups, or study. For example, the mean, variance, proportion, effect size, number of successes, number of failures, and sample size from each treatment group, combined treatment group, or study, may be used as data values or may be used in combination to calculate data values for the outcome of interest.

a. Meta-analysis protocol:

Procedures for the meta-analysis should be provided in the SR protocol which should include a complete statistical analysis plan with sufficient details to address the type of outcome to be analyzed (e.g., mean, proportion, score), the model or statistical method (e.g., generalized linear mixed model, Kaplan-Meier curves), and any factors to be included in the analysis (fixed effects, random effects, etc.). The statistical analysis plan should also include details and criteria to address the following elements: the power of the meta-analysis, investigation of heterogeneity, investigation of sensitivity of the findings, publication bias, and decision rule.

i. The power of the meta-analysis

The protocol should include a justification for a sample size sufficient to achieve the desired statistical power (typically this is 80 percent). The ability of the meta-analysis to provide evidence of effectiveness is a function of the number and types of studies that are included in the analysis, as well as the number of relevant treatment arms (i.e., groups in a clinical study delineated

[22] From draft GFI, "Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products" (November 2018). When final, this guidance will represent FDA's current thinking on this topic.

by intervention received) (Cafri, Kromrey, and Brannick 2010,[23] Hedges and Pigott 2001).[24] The sample size justification should also consider the variance and effect size of the intervention.

- Investigation of heterogeneity

  Heterogeneity (statistical heterogeneity) is evident if observed intervention effects are more different from each other than expected due to random error alone. Heterogeneity may exist if there is variability among the studies included in the SR. Variability in intervention effects may be due to clinical diversity (i.e., variability in the subjects, intervention types, and outcomes studied), methodological diversity (i.e., variability in study design, analysis method, and risk of bias), or both.

  Investigation of heterogeneity (within- and between-paper heterogeneity) may be based on Cochran's Q-statistic and Higgins I-squared value as described in the Cochrane Handbook (Higgins and Green 2011).[25] If these values indicate heterogeneity, then an investigation of the most appropriate mixed effects model is needed. If heterogeneity is not found, then a statistical analysis using a fixed effects model may be most appropriate.

- Investigate the sensitivity of the findings

  Study conclusions should be based on a primary statistical analysis described in the protocol. However, an SR with a meta-analysis often involves a sensitivity analysis which is an investigation of the impact decisions made during the study design process (i.e., study inclusion criteria, outcome metrics, and analysis methods) may have on study conclusions.

  A discussion of the results of a sensitivity analysis should also provide information to enhance the conduct and decision-making process of future related studies.

- Publication bias

  Publication bias occurs when the decision to publish or not publish the

[23] Cafri, G., J. D. Kromrey, and M. T. Brannick. 2010. "A Meta-Meta-Analysis: Empirical Review of Statistical Power, Type I Error Rates, Effect Sizes, and Model Selection of Meta-Analyses Published in Psychology." *Multivariate Behav Res* no. 45 (2):239-70. doi: 10.1080/00273171003680187.

[24] Hedges, L. V., and T. D. Pigott. 2001. "The power of statistical tests in meta-analysis." *Psychol Methods* no. 6 (3):203-17.

[25] Higgins, P.T., and S. Green. 2011. "Cochrane Handbook for Systematic Reviews of Interventions." Available at: http://handbook.cochrane.org. In: Cochrane Collaboration.

results of an individual study is influenced by the outcome of the study; for example, studies that report a large effect size or beneficial therapeutic effect may be published, while studies that show no effect or a very small effect size may not be published. Funnel plots and Egger's regression are examples of analyses which may be performed to detect and evaluate publication bias. The criteria for interpreting publication bias should be defined in the protocol.

- Decision rule

  Criteria on which a study conclusion (for safety and/or effectiveness) will be based should be included in a meta-analysis. Data analysis results, safety information, and the results of any bias investigation should be considered.

5. Submitting the SR and meta-analysis to CVM

The SR (and its accompanying meta-analysis, if applicable, referred to as an SRMA) should be submitted as a technical section data submission (STARS code "P"). Similar to other data submissions, sponsors should submit a final study report which provides a description of the materials and methods, results, statistical analysis (if applicable), and conclusions of the study. The final study report should include: a summary of the literature search, including the search criteria; numbers of publications/reports retrieved; a full accounting of the process of inclusion/exclusion during the screening and eligibility phases of the study; and a summary of all protocol deviations. In addition, a copy of the protocol with all amendments and the full statistical analysis should be attached to the final study report. Copies of raw data should be provided and should include the electronic databases identifying all studies retrieved from the literature search, identification of studies meeting screening and/or eligibility criteria, identification of excluded studies and reason for exclusion, data extracted from the studies included in the final literature review and meta-analysis, documentation of any protocol deviations including their impact on the study, and the qualifications of the investigator and any other key personnel involved in the study. The full text of study reports and publications included in the final literature review or meta-analysis should also be provided. All non-English publications must be submitted with complete and accurate English translations (21 CFR 514.1(a)).

In some cases, it may be appropriate and more efficient to submit the SR in two phases. The first phase could include information related to the conduct of the study through the eligibility phase. This will allow CVM and the sponsor to agree on the database that is used for data extraction and statistical analysis. The second submission could include the final study report and copies of all raw data as described above.

6. Labeling

Draft labeling (for example, a product's package insert) is submitted during review of

target animal safety and effectiveness technical sections and should be submitted with literature-based technical sections as well. Draft labeling language should adequately summarize the safety and effectiveness findings (for example, target organ toxicity, observed adverse events, percent effectiveness) as supported by systematic literature reviews and meta-analyses included in the submission. However, full accounting or listing of individual publications as presented in SRs and meta-analyses is not necessary in draft labeling.

IV. SPECIFIC PROCESSES AND APPROVAL REQUIREMENTS

A. Early Information

In the early stages of drug evaluation, scientific literature can help guide the discussion of the feasibility of a drug's development for a particular indication and identify potential issues that may be addressed as part of safety or effectiveness studies. Information to support these early stages of development may be presented in various ways, such as material included in an initial Investigational New Animal Drug (INAD) file submission, a presubmission conference request, or to support a protocol.

At this early stage in development, CVM does not expect literature reviews to be exhaustive. A quantitative synthesis (e.g., SRMA) is not necessary. Rather, a literature review at this stage should be of sufficient scope to provide an understanding of the novel issues the sponsor wishes to introduce and appropriately targeted to the goal of the submission. Each review will be different, depending on the issues the sponsor wishes to discuss with CVM. These issues may include: the drug's characteristics (metabolism, receptors, mode of action); the suitability of the indication; the reliability of endpoints for establishing effectiveness; highlighted data gaps that would be filled by a proposed study; and/or support for innovative study designs to demonstrate safety or effectiveness.[26]

1. Using Literature in the Early Stages of Drug Development

Literature may be used as part of the initial submissions to an INAD file to address considerations such as:

- Discuss the suitability of a novel indication:
  - Is it reasonable to believe the drug may have the proposed effect?
  - Is the effect measurable?
  - Is the effect observable to the end user?
  - Does the indication have utility to the end user?
  - Could the indication be considered false or misleading? (FD&C Act

[26] A more comprehensive discussion of the goals and types of information for these early development discussions is presented in the CVM Program Policy and Procedures Manual 1243.2200 Submission and Review of Early Information (EI) Prior to Presubmission Conferences and Protocol Review.

section 502(a))[27]

- Provide information on metabolism or mode of action: this information may be useful to support a novel indication or highlight potential safety issues or systems at risk.
- Discuss similarities to and differences from other approved products.
- Identify gaps in existing data.
- Characterize the target population: a particular class, age, or physiologic state (e.g., lactating dairy cows, growing calves).
- Support the choice of the dosage for the development of safety and effectiveness studies: literature may be used to characterize the critical aspects of the dose-response relationship for those parameters relevant to the proposed indication.
- If considering pursuing a systematic review/meta-analysis approach to support approval, a scoping review of the literature during the early development phase generally will be useful to assess the feasibility of that approach. Refer to section III.B.2. *Scoping Review* for additional information on scoping reviews. Scoping reviews are useful to:
  - Determine availability of literature
  - Refine the research question(s)
  - Develop inclusion/exclusion criteria
  - Identify gaps in existing knowledge
  - Define appropriate comparators (control groups)

2. To Support Elements of a Protocol

- Define and support the use of an endpoint as a well-defined and reliable means to evaluate effectiveness.
- Narrow the scope of a study.
- Define/justify the enrollment population for a study (i.e., inclusion and exclusion criteria).
- Establish the adequacy of infection or infestation for dose confirmation studies for antiparasitic drugs (see GFI #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations" (October 2011)). Published literature may provide some or all of the necessary information to enable a sponsor to justify a particular level of infection and distribution of infection among control animals as part of the development of a study protocol.

[27] Section 502(a) of the FD&C Act provides that a drug is misbranded if its labeling is false or misleading in any particular.

- Establish the prevalence of a disease condition (used to estimate size of test population).
- Define the current standard of care for a condition. For some drug approvals, sponsors intend to demonstrate that a new animal drug provides an increased benefit over a current standard of care. In these cases, the standard of care for a particular disease or pathologic condition is based on the scientific literature and sound and accepted professional judgment. Some examples may include the use of a pain-relieving drug in addition to standard anesthetic regimens to control post-operative pain or the addition of a drug to treat heart failure in addition to standard medication(s) to treat the condition.
- Provide background pharmacology information (receptor interactions, concentration/time dependent effects, absorption/distribution/metabolism/elimination (ADME), formulation release characteristics, and prandial considerations may be useful for understanding how the drug achieves its effect and to identify potential hazards).
- Identify properties of the formulation that may affect its safety or effectiveness, such as a modified release profile or the use of nano-materials.

B. Generic Animal Drugs

1. ANADA/and Generic INAD (JINAD) Files:

Approval of an ANADA requires submitting data to satisfy six technical sections. Systematic review and meta-analysis (SRMA) would not be appropriate for addressing the majority of these technical sections. A more limited set of references from the literature may be acceptable to supplement part of the requirements for these technical sections. Appropriate use of the literature, or SRMA, in addressing the requirements of the applicable technical sections may be as follows:

- Human Food Safety/Withdrawal period information: refer to section IV.F. *Human Food Safety* of this GFI pertaining to Human Food Safety decisions
- Labeling: the generic sponsor will copy the currently approved label of the reference listed new animal drug (RLNAD)
- CMC: refer to section IV.C. *Chemistry, Manufacturing, and Controls* of this GFI pertaining to CMC review
- Environmental Impact: refer to GFI #89 (VICH GL6), "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I" (March 2001) and GFI #166 (VICH GL38), "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase II" (January 2006) pertaining to environmental assessments
- Bioequivalence: because of the uniqueness of formulations attributable to manufacturing processes and formulation, etc., each generic sponsor will have to submit formulation and/or active pharmaceutical ingredient (API) specific data to address the bioequivalence of their product with respect to that of the

RLNAD. CVM considers it highly unlikely that there would be literature regarding the exact formulation using the same manufacturing process for a specific generic drug product. Therefore, an SR and meta-analysis would not be appropriate or acceptable for demonstrating bioequivalence without confirmation that the formulation of the proposed generic drug product is the same as the RLNAD. However, literature may be used to justify decisions made in a determination of bioequivalence, or to confirm that an unexpected result is appropriate for that API or product.

2. Suitability Petitions:

- Suitability petitions allow prospective applicants to request permission to submit an application for a generic new animal drug product that differs from an RLNAD in certain specified ways (FD&C Act section 512(n)(3)). Sponsors may use information from literature to support a suitability petition. As a general matter, literature submitted in support of a suitability petition does not need to meet the requirements for an SRMA.

C. Chemistry, Manufacturing, and Controls

In order to approve new animal drug products, including those where safety and effectiveness is established by reference to publications in the scientific literature, all relevant information as described in 21 CFR 514.1(b)(4) and (b)(5) must be submitted to support the CMC technical section. Release and stability specifications are a critical aspect of the CMC technical section and verify the identity, strength, quality, purity, and potency of the drug product. Typically, the drug product used in the safety and effectiveness studies and the marketed drug products are tested using the same set of release and stability specifications. This establishes a link between the clinical studies and the marketed product and provides assurance that the marketed product will have the same product performance as the drug product used in the clinical studies. If publications in the scientific literature are used to support the safety and effectiveness technical sections, the following information should be considered to determine if a link between the proposed CMC specifications and the published studies can be supported:

- Was the specific proposed commercial formulation used in the literature?
- Were the lots used in the published study tested according to the proposed release testing and are the results of the release testing published or available for review?
- Does the sponsor have experience with manufacturing the product under current good manufacturing practices (CGMP) (FD&C Act section 501(a)(2)(B)) conditions and can historical data be provided to support the proposed release and stability specifications?

If a direct connection cannot be made between the proposed commercial formulation and the published literature (e.g., a different drug product was used in the studies described in the published literature), the sponsor should consider:

- If the literature indicates that a specific safety (e.g., byproduct of manufacturing

process or stability that could lead to toxicity) or effectiveness (e.g., narrow therapeutic range) issue exists that should be controlled in the manufacturing process.

- If bridging studies (e.g., bioequivalence) have been performed to demonstrate the relevance of the information in the literature to the proposed drug product.
- Depending on the complexity of the drug product and the manufacturing process, if general specifications (e.g., assay 90-110 percent), based on appropriate VICH or CVM guidance documents or United States Pharmacopeia (USP) chapters or monographs, can be utilized.

If there are any critical quality attributes of the drug product where a link to clinical safety and effectiveness data is needed (e.g., release characteristics, new dosage form, bioassay, viability), reference to published scientific literature alone may not be sufficient to support the approval of the new animal drug product.

D. Effectiveness

1. Scope of Use

Literature may be used to fulfill all or part of the requirements for the effectiveness technical section for new animal drug product approvals or the reasonable expectation of effectiveness (RXE) technical section for conditional new animal drug product approvals. For example, SRs and meta-analyses may provide substantial evidence of effectiveness for either all or a portion of the indication. Individual literature reports may provide information to satisfy a particular data gap, lead to the identification of a data gap, or satisfy RXE.

The degree of support that literature submissions may provide toward fulfilling requirements for substantial evidence of effectiveness or reasonable expectation of effectiveness cannot fully be determined until after review of the submission and review of other technical information such as chemistry and pharmacokinetic data. CVM encourages sponsors to request meetings early in the approval process to discuss options for presenting the available information, designing protocols, and determining viability of a path forward.

2. Dosage Characterization

Dosage characterization is the justification of the dosage (dose or dose range, dosing frequency, and the dosing duration) and a characterization of the critical aspects of the dose-response relationship related to each intended use and associated conditions of use. Dosage characterization is part of the effectiveness technical section of an INAD file and may be derived from dose titration studies, pilot studies, foreign studies, scientific literature, or other sources. Scientific literature, including individual or multiple sources, may be used to support a portion or all of the justification of 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. If the use of literature to fulfill a portion or all other technical sections is contemplated, any literature used to characterize the dosage should be identified and evaluated in an independent manner to avoid biasing a future systematic review.

3. Substantial Evidence of Effectiveness

a. Regulatory standards:

Effectiveness must be demonstrated by substantial evidence consisting of one or more adequate and well-controlled studies (FD&C Act sections 512(d)(1)(E) and (d)(3); 21 CFR 514.1(b)(8)(ii); 21 CFR 514.4(a); and 21 CFR 514.117). Substantial evidence is defined in 21 CFR 514.4(a) as "evidence consisting of one or more adequate and well-controlled studies … on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the 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 labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect."

An SR intended to demonstrate substantial evidence of effectiveness of a new animal drug for an original or supplemental NADA must be adequate and well-controlled (21 CFR 514.4(a)). The protocol for an SR should provide details relative to the study design, conduct, and analysis in accordance with the characteristics of an adequate and well-controlled study (21 CFR 514.117(a)-(b)). When using an SR to demonstrate substantial evidence of effectiveness, the review objective is generally the same as a traditional clinical study (e.g., the objective of the study will be to evaluate the effectiveness of a specific formulation of drug, given at a specific dosage, for specific indications (and conditions of use) in specific species/classes).

Things to consider when developing a proposal for an SR to demonstrate substantial evidence of effectiveness:

- The regulations (21 CFR 514.4) require a demonstration of substantial evidence of effectiveness for the new animal drug, and 21 CFR 514.117(b)(3) requires that adequate and well-controlled studies be conducted with "…a new animal drug that is produced in accordance with appropriate manufacturing practices, which include, but are not necessarily limited to, the manufacture, processing, packaging, holding, and labeling of the new animal drug such that the critical characteristics of

identity, strength, quality, purity, and physical form of the new animal drug are known, recorded, and reproducible, *to permit meaningful evaluations of and comparisons with other studies conducted with the new animal drug"* [emphasis added]. Therefore, for SRs, as is the case for other types of adequate and well-controlled studies, critical factors in the study design are the identity, strength, quality, purity, physical form, and critical quality attributes[28] of the new animal drug product used in the study. All individual studies included in the SR should have sufficient detail to confirm the identity of the drug product. In some cases, author contact may facilitate the retrieval of additional product specific information (lot numbers, batch numbers, certificates of analysis) useful for the SR and confirmation of appropriate manufacturing practices.

- Generally, if studies using a proposed new animal drug product's final formulation are not available for inclusion in the SR (and accompanying meta-analysis, if applicable), this will limit the applicability of the information.[29] The acceptability of published studies will depend on the complexity of the formulation, how much control the sponsor had over the manufacturing process, etc. CVM will evaluate the drug product used in each published study included in the SR (and accompanying meta-analysis, if applicable) using information on the identity, strength, quality, purity, and physical form. The level of documentation and known information is usually not the same as what is included in a single adequate and well-controlled study submitted to CVM with raw data. However, the assessment of how much a formulation and other critical quality attributes can deviate from the proposed/final formulation is generally the same regardless of the type of study (SRMA or single prospectively designed study).

- As noted in section III.B.3. *Critical Factors*, literature using the proposed final formulation manufactured by or for the sponsor provides the best, most rigorous evaluation and the highest evidentiary weight. If a sufficient number of studies using an acceptable formulation are not available or a connection to information found in the CMC technical section cannot be made, the SR approach will be unlikely to demonstrate substantial evidence of effectiveness.

- The sponsor should provide CVM with an assessment of the information, a meaningful evaluation of the new animal drug used in the published

[28] ICH Q8(R2), "Pharmaceutical Development" (November 2009).

[29] Formulation changes to a drug product may occur over time and will be evaluated on a case-by-case basis to determine their potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors relate to the safety or effectiveness of the drug. These principles are discussed in more detail in Guidance for Industry #83, "Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA" (May 2007). In some cases, studies will be necessary to establish the equivalence of different formulations (e.g., pharmacokinetic studies, and/or clinical studies as appropriate).

report included in the SR (and accompanying meta-analysis, if applicable) and a justification that it is appropriate to use the data generated in the study along with other studies in the SR (and accompanying meta-analysis, if applicable). The decision about the value of the information from the published studies to the SR (and accompanying meta-analysis, if applicable) will be made with the collaboration of ONADE's Division of Manufacturing Technologies and the target animal review team.

- Adequate and well-controlled studies, including SRs, include the use of methods to assess the animal response to the use of the new animal drug that are well defined and reliable (21 CFR 514.117(b)(8)). Sponsors should consider whether there are a sufficient number of studies which report the appropriate endpoint(s) in a consistent manner which would allow for quantification of the effect of the new animal drug.

b. Protocol considerations specific to effectiveness:

- Review question: The review question should closely match the objectives of the study and follow the format described in section III.B.3.b.i. *Developing the Review Question* of this guidance. In general, effectiveness study review questions follow the format: "Evaluation of the effectiveness of [drug product and dose if appropriate] for [indication] as compared to [control type] in [species/class/animal age as appropriate]."

- Definition of the control: Please refer to section III.B.3.b.ii. *Writing the protocol (Control Type)*.

- Inclusion/Exclusion Criteria:

  Examples of screening inclusion/exclusion criteria which may be assessed based on the title, abstract, and/or key words include:

Screening Inclusion	**Screening Exclusion**
Study types: Complete reports (published or unpublished) on randomized controlled trials (RCTs), cluster RCTs, and select non-randomized controlled studies	Incomplete reports (abstracts and reviews), or insufficient information to assess these criteria (incomplete reports may not be excluded if full information could be obtained from the study investigator)
Study includes intended target animal species and class	Study includes animals that are not representative of the target animal species and class
Use of the drug product of interest (at screening phase, identification of active ingredient may be sufficient)	Drug product of interest not a part of the study

Examples of eligibility inclusion/exclusion criteria based on assessment of the full text of the publication:

Eligibility Inclusion	Eligibility Exclusion
Drug product as defined in the protocol	Study does not include drug product as defined in protocol, or publication does not provide sufficient information to identify the drug product (unable to confirm formulation used in the study)
Study uses intended label dosage (dose, frequency, and route of administration)	Dosage used in study inconsistent with the intended label dosage
Study includes the use of acceptable concurrent therapies (e.g., the studies may employ concurrent therapies per the current standards of care; however, these considerations should be described clearly within the protocol.)	Study includes the use of concurrent therapy that may confound the effectiveness evaluation
Study designed to evaluate endpoint(s) of interest	Study not designed to evaluate endpoint(s) of interest

Screening and eligibility inclusion and exclusion criteria should only evaluate whether the measurement of an effectiveness outcome is present and should not specify a particular effectiveness outcome for inclusion in the effectiveness database. For example, studies that do not demonstrate the desired level of effect or that report a poor effectiveness outcome should not be excluded from the effectiveness database.

- Basis of study conclusion:

  The protocol should clearly state the criteria on which study conclusions will be based. The study objectives and the statistical analysis results should be considered when defining the criteria. For example, a threshold for an effect size or a threshold for the limits of a confidence interval for the effect size could be used as criterion. In addition, the study conclusion should also consider bias investigation results.

4. Reasonable Expectation of Effectiveness

Section 571 of the FD&C Act (21 U.S.C. 360ccc) provides for a qualified approval pathway, open only to certain qualifying new animal drug products based on indication and type, called conditional approval. Conditional approval allows a sponsor to legally market a new animal drug after demonstrating the drug is safe and manufactured in accordance with the full approval standards, and that there is a reasonable expectation of effectiveness. To obtain conditional approval, all technical sections must be complete except the effectiveness technical section, which is

replaced with RXE. The sponsor can market the conditionally approved new animal drug product for up to 5 years while gathering the remaining data required to demonstrate substantial evidence of effectiveness. The pathway requires annual renewal of the conditional approval to determine whether the sponsor is making sufficient progress toward meeting the effectiveness standard for full approval. Literature may be used as one of the pathways to support RXE. Screening and eligibility criteria for publications that may be used to support RXE are generally the same as for substantial evidence of effectiveness; however, the overall body of evidence may be smaller and information gaps may still be present. Full scoping or systematic literature reviews are not routinely expected but may be appropriate.

E. Target Animal Safety

1. Scope of Use

Section 512 of the FD&C Act (21 U.S.C. 360b) establishes the requirements for new animal drug approval, including target animal safety. See FD&C Act section 512(d)(1)(A), (B), and (D) (21 U.S.C. 360b(d)(1)(A), (B), and (D)).

Literature, including narrative reviews, SR, and meta-analysis, may be acceptable to fulfill all or part of the requirements for target animal safety for a new animal drug application or an application for conditional approval (see FD&C Act section 571(a)(2)(B)). Literature is most commonly used to evaluate the extent and quality of information available on the safety of a new animal drug for the proposed indication or proposed conditions of use, support the design of the target animal safety evaluation, and/or provide information to predict potential adverse effects in the target species. In some cases, literature may provide all or a portion of the information required to demonstrate whether a new animal drug is safe for the intended use and conditions of use.

CVM encourages sponsors to request meetings early in the development plan to discuss options for presenting the available information, designing protocols, and determining viability of using literature to fulfill some or all of the target animal safety requirements.

2. Preliminary Information

GFI #185 (VICH GL43), "Target Animal Safety for Veterinary Pharmaceutical Products" (April 2009), describes the use of knowledge about the pharmacology and toxicology of an investigational veterinary pharmaceutical product (IVPP) to assist in the determination of the types of studies necessary in the evaluation of the safety of an IVPP in the intended species under the proposed conditions of use; in the design (dose, frequency of dosing, overdose levels, durations of treatment, and endpoints) of such studies; and in the prediction of potential adverse effects. GFI #185 recommends the use of published literature, in addition to preliminary studies from target and non-target laboratory animal studies, as potential sources of the pharmacology and toxicology data.

A review of the published literature may provide information about the known pharmacologic and toxicological properties in target or non-target species of the drug, to include carriers, excipients, inactive ingredients, APIs, or about closely related compounds that may be useful in planning the target animal safety evaluation. Information that may be useful includes the following:

- Mechanism of action
- Mechanism of toxicity
- Toxicological syndrome/target organs or tissues
- Clinical signs of toxicity/biomarkers of toxicity
- Time of onset and duration of clinical signs of toxicity
- Variability/tolerance among animals (species, breed, class, age, or other differences)
- Severity, chronicity, and likelihood of toxic effects
- Differences by animal age/life stage/production class/breed
- Pharmacokinetics/pharmacodynamics
- Potential for drug-drug interactions
- Effects of other diseases/conditions on toxicity
- Endpoints that can be collected from other required studies
- Effects on reproduction
- Effects at the site of administration (injection, topical, etc.)

Generally, a narrative literature review or a scoping review, rather than an SR, is appropriate for presenting the pharmacologic and toxicologic information to CVM for the purposes of supporting the target animal safety development plan and the design of safety studies.

3. Literature to Satisfy Target Animal Safety Requirements

The safety of a new animal drug in the target animal is typically based on one or more non-clinical laboratory studies (margin of safety studies) and observations from field studies. As described in GFI #185, other specific studies, such as reproductive safety, injection site, or other specifically designed studies, may be needed to address the animal safety requirements. The need for these specific studies depends on the drug and the intended conditions of use.

The literature may provide information from target and non-target species, including laboratory animals, which may be used in lieu of the margin of safety study or other studies (injection site, reproductive safety, etc.) typically needed to satisfy the target animal safety requirements, a justification that typical studies (or certain endpoints within these studies) are not needed, an identification of information "gaps," or the

identification of safety observations that could be obtained during the effectiveness study(ies).

a. Margin of safety study

Typically, the margin of safety study includes multiples of the highest intended drug dosage (daily dose, frequency, and duration) where the study results demonstrate the margin of safety above the maximum dosage. The study must adequately demonstrate that the new animal drug is safe for the intended target animal/class under the proposed conditions of use, that the chosen endpoints are the most appropriate outcomes for the evaluation of safety, and that valid inferences can be drawn to the target population. The number of studies needed to assess overall safety, or a particular endpoint will depend on the size and number of studies, intended use/conditions of use, breadth of the indication, consistency of results, the quality of the studies, and/or the quality of the reporting of the studies.

In some cases, a sufficient amount of information exists in the published literature and/or in preliminary studies to either: (1) justify that a margin of safety study is not needed (negligible systemic exposure to the API and based on pre-existing knowledge in pharmacology and toxicology there is no safety concern[30]); or (2) perform an SR (+/- meta-analysis) which provides adequate information to determine the safety of the new animal drug in the target animal. The literature may provide a volume and variety of evidence that far exceeds the data traditionally available from a margin of safety study.

b. Performing an SR to satisfy target animal safety requirements

When considering literature to satisfy any or all animal safety requirements, and before developing the protocol, the sponsor should perform a high-level initial screen of available literature with considerations such as dose, formulation, endpoints appropriate for an animal safety evaluation, conditions of use, and inferential value for the target population. This screen should be performed in a way that minimizes bias in case a future SR and/or meta-analysis will be performed; the person or persons performing the high-level screening should not be involved in the design of the protocol for the conduct of the regulatory SR.

An SR of the literature may provide a broader overview of the safety of the drug in the target animal population when compared to a more comprehensive evaluation in a small number of individual animals (e.g., a laboratory margin of safety study). For some drugs and indications, an assessment under more variable conditions of use may be preferable for the evaluation of animal safety. Typical assessment of animal safety relies substantially on clinical outcomes, assessments of those outcomes, and impacts on the animal with regard to determining the

[30] Per GFI #185, even if a margin of safety study is not needed, a safety study at the site of administration is recommended.

margin of safety. Statistical analyses may be of more importance in identifying dose response trends or observations of most interest.

For an SR and/or meta-analysis to evaluate safety, the review question may be broad, to capture any abnormal observations related to administration of the new animal drug, or specific, to address a certain safety-related endpoint. An adequate target animal safety assessment will include the identification of target organs, where possible, and confirmation of the margin of safety for the labeled dosage regimen (dose, route, frequency, duration) in the intended species/class(es).

The SR should evaluate a specific formulation of drug produced in accordance with appropriate manufacturing practices. Formulation should be taken into consideration when selecting the studies that are appropriate for inclusion.

A meta-analysis may not be appropriate for all submissions that include a literature or systematic review. Other types of analyses (i.e., a multicriteria decision analysis or a weight-of-evidence analysis) or a qualitative assessment may be more appropriate. The available information should be used to determine what conclusions can be drawn, such as an evaluation of the risk of adverse events or safety concerns for the animal associated with the use of the drug at the proposed dose under the intended conditions of use, and identify any gaps remaining in the target animal safety evaluation. Using the literature to develop a hazard characterization may be adequate to frame the further studies and study designs needed to meet the target animal safety requirements. The strength of support provided by the body of available literature is useful in determining the number and type of necessary studies and the potential adverse reactions or safety impacts that may be observed. If gaps are identified, the available information can be used to inform methods used to address the gaps and the design of one or more studies to address the gaps, which include alternative or non-traditional studies. Information from the literature may be used to inform the design of the margin of safety study in an evaluation and the prediction of potential adverse effects that may occur in the target species.

4. Other Laboratory Safety Studies

For certain indications or conditions of use and for certain dosage forms, additional safety studies, such as evaluation of injection sites or application sites for topically administered drugs, a reproductive safety study, or other specific studies, may be needed in addition to a margin of safety study. Literature may be appropriate for addressing the requirements for these specifically designed studies as described in GFI #185.

a. Safety information from field studies:

Studies conducted to evaluate effectiveness may provide a source of information which addresses important safety endpoints. Studies included in an SR to address effectiveness, or the combination of sponsor-conducted studies and studies

reported in the published literature, may provide adequate information to address certain animal safety considerations.

b. Standard of conduct

CVM expects nonclinical laboratory studies intended for target animal safety to be conducted in accordance with GLPs. An SRMA for target animal safety is not considered a nonclinical laboratory study, as defined by 21 CFR 58.3, but may include one or more nonclinical laboratory studies. Generally, published studies do not state a standard of conduct and do not include the level of detail that permit assessment of all GLP requirements (or components). Depending on the question asked for the SRMA, studies of multiple types or designs may be included in an SRMA for target animal safety.

F. Human Food Safety

Published literature is normally considered in the human food safety evaluation of products regulated by CVM. Information extracted from the literature can be used either as pivotal or as corroborative information in the human food safety assessment.

1. Microbial food safety (antimicrobial resistance)

CVM's draft revised Guidance for Industry (GFI) #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (December 2022), outlines a risk assessment approach to evaluate the microbial food safety of antimicrobial new animal drugs. It states, "[w]ithin the context of risk assessment, many possible mechanisms to address the development of antimicrobial resistance resulting from the use of antimicrobial new animal drugs in food-producing animals are available to the sponsor. Alternative processes that may be more appropriate to a sponsor's drug and its intended conditions of use may be used to characterize the microbial food safety of that drug."

This guidance states the submission of current and relevant literature can be a source of quality data to characterize the hazard and to assess the risk to human health. GFI #152 also provides examples of types of data and information that may be used.

2. Toxicology and residue chemistry

CVM recommends a standard series of toxicology and residue chemistry studies (see GFI #3, "General Principles for Evaluating the Human Safety of New Animal Drugs Used in Food-Producing Animals" (June 2018)), but also accepts alternative approaches, such as risk-based or weight-of-evidence approaches that may include consideration of information from published literature. Literature-based, scientifically valid evidence is often considered as supportive information in the review process. Literature-based information may be accepted as the sole basis to satisfy toxicology and residue chemistry requirements on a case-by-case basis. The type of information (level of details, study and data quality, etc.) in the published literature should be adequate to allow CVM to address a specific toxicology or

residue chemistry question with reasonable certainty or be sufficient to meet the toxicology and residue chemistry requirements.

V. GLOSSARY

For purposes of this guidance, the following definitions apply:

Active control: The new animal drug is compared with known effective therapy. The use of this control is appropriate when the use of a placebo control or of an untreated concurrent control would unreasonably compromise the welfare of the animals. Similarity of the new animal drug and the active control drug can mean either that both drugs were effective or that neither was effective. The study report should assess the ability of the study to have detected a difference between treatments. The evaluation of the study should explain why the new animal drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control (21 CFR 514.117(b)(4)(iii) and GFI #204, "Active controls in studies to demonstrate effectiveness of a new animal drug for use in companion animals" (December 2015)).

Attrition bias: Bias due to systematic differences between treatment and comparison groups in withdrawals or exclusions from the results of a study (Hoffmann et al. 2017).[31]

Citation bias: Citation bias refers to bias due to the citation or non-citation of research findings, depending on the nature and direction of the results (https://methods.cochrane.org/bias/reporting-biases – Accessed on December 6, 2022).

Critical Quality Attribute (CQA): a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product.

Detection bias: Detection bias refers to bias due to systematic differences between groups in how outcomes are determined (Hoffmann et al. 2017).

Grey literature: (1) studies not indexed in commercial bibliographic databases[32]; (2) materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels. Common grey literature publication types include reports (annual, research, technical, project, etc.), working papers, government documents, white papers and evaluations[33]; (3) conference proceedings; and (4) for the purposes of this guidance, grey literature may also include research produced by the sponsor (e.g., pilot studies and other proprietary reports).

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[31] Hoffmann, S., R. B. M. de Vries, M. L. Stephens, N. B. Beck, Haam Dirven, J. R. Fowle, 3rd, J. E. Goodman, T. Hartung, I. Kimber, M. M. Lalu, K. Thayer, P. Whaley, D. Wikoff, and K. Tsaioun. 2017. "A primer on systematic reviews in toxicology." *Arch Toxicol* no. 91 (7):2551-2575. doi: 10.1007/s00204-017-1980-3.

[32] See footnote 19 on p. 12.

[33] "Grey Literature." Available at: https://en.wikipedia.org/wiki/Grey_literature - Accessed on March 2, 2023.

Historical control: The results of treatment with the new animal drug are quantitatively compared with experience historically derived from the adequately documented natural history of the disease or condition or with a regimen (therapeutic, diagnostic, prophylactic) whose effectiveness is established in comparable animals. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies in which the effect of the new animal drug is self-evident or studies of diseases with high and predictable mortality, or signs and symptoms of predictable duration or severity, or, in the case of prophylaxis, predictable morbidity (21 CFR 514.117(b)(4)(iv)).

Intervention: The act of intervening, interfering, or interceding with the intent of modifying the outcome. In medicine, an intervention is usually undertaken to help treat or cure a condition (https://www.medicinenet.com/script/main/art.asp?articlekey=34214).

Language bias: The publication of research findings in a particular language, depending on the nature and direction of the results (http://methods.cochrane.org/bias/reporting-biases).

Location bias: The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results (http://methods.cochrane.org/bias/reporting-biases).

Meta-analysis: A meta-analysis is the statistical combination of results from multiple individual studies.

Negative control (untreated concurrent control): The new animal drug is compared with the absence of any treatment. The use of this control may be appropriate when objective measurements of effectiveness, not subject to observer bias, are available (21 CFR 514.117(b)(4)(ii)).

Non-inferiority: A Non-Inferiority (NI) study is designed to demonstrate the effectiveness of a new drug by showing that the new drug is no worse than a known effective therapy based on an appropriate endpoint (see GFI #204).

Outcome bias: The selective reporting of some outcomes but not others, depending on the nature and direction of the results (http://methods.cochrane.org/bias/reporting-biases).

Performance bias: Performance bias refers to bias due to systematic differences between groups in the care that is provided or in exposure to factors other than the interventions of interest (Hoffmann et al. 2017).

Placebo control: The new animal drug is compared with an inactive preparation designed to resemble the new animal drug as far as possible (21 CFR 514.117(b)(4)(i)).

Raw data: Any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study (21 CFR 58.3(k)).

Research question: The objective of the scoping or systematic review that defines the parameters of the study from which search terms and inclusion/exclusion criteria are created.

Reporting bias: Reporting bias is introduced when only selected outcomes are reported (applying both to systematic reviews and primary studies) (Hoffmann et al. 2017). Reporting bias occurs when dissemination of study results is influenced by the study outcome. Reporting bias includes the following types of bias: publication bias, time lag bias, location bias, citation bias, language bias, and outcome bias (http://methods.cochrane.org/bias/reporting-biases).

Review question: A well-focused question stating the objective of the review.

Risk of bias: The degree of bias susceptibility of a study (Hoffmann et al. 2017).

Scoping review: The process of systematically and qualitatively synthesizing available evidence. Scoping reviews have been described as a process of mapping the existing literature or evidence base (Armstrong et al. 2011).

Selection bias: Selection bias refers to bias due to systematic differences between baseline characteristics of the groups that are compared (Hoffmann et al. 2017).

Statistical bias: For a point estimator, statistical bias is defined as the difference between the parameter to be estimated and the mathematical expectation of the estimator. Statistical bias can result from methods of analysis or estimation. For example, if the statistical analysis does not account for prognostic factors (variables known to affect the outcome variable), then it is possible that the estimated treatment effects will be biased (Hoffmann et al. 2017).

Substantial evidence of effectiveness: Evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the 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 labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect (21 CFR 514.4(a)).

Superiority: the primary objective of a superiority study is showing that the response to the intervention is superior to a comparator (control).[34]

[34] ICH Topic E9. Statistical Principles for Clinical Trials. 1998. European Medicines Agency. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf.

Systematic review: an overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardized methods to identify and critically appraise relevant research, and to collect, report, and analyze data from the studies are included in the review.[35]

Time lag bias: time of publication depending on the results (Hoffmann et al. 2017).

[35] European Food Safety Authority. Guidance of EFSA: Application of systematic review methodology to food and feed safety assessments to support decision making. Available at: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2010.1637 - Accessed on March 2, 2023.

VI. Appendix

Example of screening and eligibility database

Column ID	Column Data	Definition
Ref	# (A, B, C)	A=Original search, B=result of hand-searching, C=result of author contact
Year	#	Year of publication
Auth	Last, First Middle	Name of first author
Title	Study Title	Full title of study as listed in publication
Citation	Full reference	Complete citation for the reference
Type	RCT, cRCT, NRC, NRTS, NRCS, O	RCT=randomized controlled trial, cRCT=cluster randomized controlled trial, NRC=non-randomized, controlled before/after study, NRTS=non-randomized interrupted time series, NRCS=non-randomized case series, O
Full Text	Y/N	Y=Full text available N=Full text unavailable
SC1 (Screening Criterion 1)	0 or 1	0=meets screening criterion 1=does not meet screening criterion
SC2 (Screening Criterion 2)	0 or 1	0=meets screening criterion 1=does not meet screening criterion
SC3 (Screening Criterion 3)	0 or 1	0=meets screening criterion 1=does not meet screening criterion
SC4 (Screening Criterion 4)	0 or 1	0=meets screening criterion 1=does not meet screening criterion
PE1 (Primary eligibility criterion 1)	0 or 1	0=meets primary eligibility criterion 1=does not meet primary eligibility criterion
PE2 (Primary eligibility criterion 2)	0 or 1	0=meets primary eligibility criterion 1=does not meet primary eligibility criterion
PE3 (Primary eligibility criterion 3)	0 or 1	0=meets primary eligibility criterion 1=does not meet primary eligibility criterion

Column ID	Column Data	Definition
PE4 (Primary eligibility criterion 4)	0 or 1	0=meets primary eligibility criterion 1=does not meet primary eligibility criterion
Final Assessment	I or E	I=Include (meets screening, and eligibility criteria) E=Exclude (does not meet on or more screening or eligibility criterion)

Example of data extraction database for eligible studies used in meta-analysis for effectiveness studies). This table provides an example listing of information that would be extracted from the individual publications to create the data extraction database. The first column includes a list of variables that would become column headings in the database, the second column includes examples of data extracted from the publication for each column in the database, and the third column provides additional clarification for or definition of the variable or data coding.

Column ID	Column Data	Definition
Ref	# (A, B, C)	A=Original search, B=result of hand-searching, C=result of author contact
Year	#	Year of publication
Auth	Last, First Middle	Name of first author
Title	Study Title	Full title of study as listed in publication
Citation	Full reference	Complete citation for the reference
Type	RCT, cRCT, NRC, NRTS, NRCS	RCT=randomized controlled trial, cRCT=cluster randomized controlled trial, NRC=non-randomized, controlled before/after study, NRTS=non-randomized interrupted time-series, NRCS=non-randomized case series
Study population (ie., animal class, breed, age, etc., as applicable to the study.)	Establish codes as needed for the systematic review to define the participants in the study (e.g., by animal class, age, gender, reproductive status)	Include definitions as needed
Country where study conducted	US, CA, EU, Other	US=United States, CA=Canada, EU=Europe; Other=Other

Column ID	Column Data	Definition
Exp.	Number	Experiment number within paper
Group	T, C	T=treatment; C=control as defined in study methodology
Treatment arm	A, B, C,…Z, AA, BB, CC,…N/A	Letter indicates a unique identifier for the study arm within the meta-analysis treatment group. Within a publication number (1, 2, 3,…) or within a study that is within a publication, treatment arms should have different letters (A, B, C,…). If the study arm is not used within a meta-analysis treatment or control group, then "N/A" will be placed in the column.
Control arm	A, B, C,…Z, AA, BB, CC,…N/A	Letter(s) indicate a unique identifier for the study arm within the meta-analysis treatment group. Within a publication number (1, 2, 3,…) or within a study that is within a publication, treatment arms should have different letters (A, B, C,…). If the study arm is not used within a meta-analysis treatment or control group, then "N/A" will be placed in the column.
Enter meta-analysis	0=excluded from meta-analysis, 1=included in meta-analysis	This row may be used to define if data from this study will be entered into systematic review software such as Review Manager[36]
Treated	N	Total number of animals originally assigned (enrolled) in the treatment arm at the start of the study
Evaluable	N	Total number of animals used in the statistical analysis for the endpoint at treated the end of the study
Missing	%	((# enrolled - # with data reported)/# enrolled)) x100
Drug Product name	Product	Proprietary name

[36] https://community.cochrane.org/help/tools-and-software/revman-5 – Accessed March 2, 2023.

Column ID	Column Data	Definition
Concentration	Conc	Drug product concentration
Manufacturer	Manf	Drug product manufacturer
Batch/Lot	#/#	Batch or lot number
Expiration date	Exp	Drug product expiration date
ROA	Abbreviations for route of administration	Define routes of administration
ROA Code	1, 2, 3, 9999=unknown	Define routes of administration as needed, 9999=unknown
Dose	# mg	As defined in protocol
Conc med		Concurrent medication List
Outcome	Abbreviations for outcome measure(s)	Outcome measure definition(s)
Timing	Hrs, days, etc.	Timing of outcome measure
Endpoint success	#	Number of animals for which outcome defined as a success
Endpoint failure	#	Number of animals for which outcome defined as a failure failed
Control type	negN, negS, plb, active, hist, none	negN=negative control, no treatment
Exp. unit	animal, pen	
Randomized	Y, N, UK	yes, no, unknown
Observer blind	Y, N, UK	yes, no, unknown
Quality standard	GCP, GLP, GSP, unk	Quality standard of the study, if provided
QA	Y, N, UK	Quality assurance used, if provided
CV	Y, N	Curriculum Vitae of investigator
Person	yes, no, unknown	
Raw data	Y, N, UK	yes, no, unknown
Raw data code	S=summarized, R=raw Data	
Study	Objective	
Study observations	methodology, timing, clinical exam, clinical pathology, necropsy, histopathology	
Endpoint	addl details, method of calc	

Column ID	Column Data	Definition
Safety observations	Adverse Event description	
Statistical considerations	Description	
Insert rows as necessary to describe bias assessment; multiple rows may be necessary, depending on the types of bias evaluated in the systematic review	Free text referencing other columns related to bias assessment, e.g., rows 'Randomized,' 'Observer blind,' 'Study observations,' 'Group' and other rows as necessary	To report study specific bias such as selection bias (e.g., were animals randomized; if so, were the methods appropriate?); reporting bias (e.g., were assessment methods selectively reported based on outcome?); and stats bias (e.g., was the variability clearly defined? Were there missing summary stats?)
Bias code (repeat this row for different types of bias)	1=high risk of bias, 2=low risk of bias/no impact expected, 3=unclear risk of bias	