Australian Government

Australian Pesticides and Veterinary Medicines Authority

Efficacy and Target Animal Safety Overview (Executive Summary)

Instructional Template

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Comments and enquiries regarding copyright:

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
GPO Box 574
Canberra ACT 2601 Australia

Telephone: +61 2 6770 2300
Email: communications@apvma.gov.au.

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Instructions

The purpose of the Efficacy and Target Animal Safety Overview (Executive Summary) is to provide a brief outline of the efficacy and target animal safety elements of the application and to lead the APVMA assessors through the dossier. Applicants must familiarise themselves with the data requirements and criteria specified in the APVMA Efficacy and target animal safety general guideline (Part 8) and any relevant specific guideline. This instructional template is intended to assist applicants in preparing an Efficacy and Target Animal Safety Overview (Executive Summary) that is comprehensive, appropriately structured, and fit for purpose. The overview should contain general information on the product, and a summary of all data in the application.

Guidance is provided on how to present this information in each section of the Efficacy and Target Animal Safety Overview (Executive Summary) of your application, along with examples highlighted in yellow to help you. Depending on the type of your application, some sections may not be relevant to you. In cases where you consider certain sections are not relevant or you are not providing data as recommended, you should justify how or why the APVMA can be satisfied the product meets the safety or efficacy criteria without the information outlined in these sections.

Tables are provided as examples and may be adapted to suit the product being evaluated (columns can be added or deleted). Moreover, some tables are not relevant for all products or all submission types and should be added or deleted as appropriate.

For new and innovative products new sections and/or tables can be added as appropriate.

Adherence to this guidance is not mandatory but is **strongly recommended** to ensure all the necessary information is provided and presented in a manner that will assist the APVMA in the evaluation of your application and reduce the likelihood for requests for further information during the assessment.

A note on scientific argument and scientific references

Where published literature is relied upon to support claims in-lieu of product-specific studies, it should be incorporated in the relevant sections (e.g. dose determination, pharmacokinetics). The relevance of each cited scientific publication to the application should be clearly articulated to facilitate assessment.

Where a substantial number of references (e.g. more than 10) are relied upon within a given section, applicants should provide a summary table that lists each reference, outlines the key findings, and clearly identifies its contribution to supporting the purpose of the application, consistent with the format outlined below.

Table X: Provide an overview of published papers relied upon and relevance to the proposed product

Year	Author/Title	Formulation Used	Summary	Purpose: What it establishes
Example: 2013.	Gonzales *et al*. Interleukin-31: its role in canine pruritus and naturally occurring	N/A	This prospective clinical trial administered IL-31 to Beagles via several routes (intravenous (IV), subcutaneous (SC) or intradermal (ID))	This was a useful study to demonstrate the role of IL-31 in pruritic conditions in the dog.

Year	Author/Title	Formulation Used	Summary	Purpose: What it establishes
	canine atopic dermatitis. Vet Dermatol 24: 48–e12		and observed that IL-31 induced significant pruritic behaviour increases, compared to placebo controls. The study also reported that IL-31 was detectable in 57% of dogs with naturally occurring AD, but were below limits of quantification (LOQ) in normal dogs.	Supportive of efficacy.
2013	Cosgrove *et al.*, Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. Vet Dermatol 24, 479–e114.	Oclacitinib (Apoquel®) Formulation details not provided.	This prospective placebo-controlled study investigated the efficacy and safety of oclacitinib in 436 client-owned dogs with (presumptive) AD. Oclacitinib (0.4-0.6 mg/kg PO bid) for 7 days was assessed by an owner VAS and the treating veterinarian VAS. There was a significant (P<0.0001) improvement in VAS and pruritus score (7.58 to 2.59 cm) on each day. Diarrhoea and vomiting had the same incidence in both groups.	While not the same formulation as the proposed product, showed that JAK inhibitors provided rapid and safe relief of allergic dermatitis in dogs. Supportive of efficacy.

Similarly, where scientific arguments are used to address data gaps, these should be included in the relevant sections. Such arguments must be evidence-based, supported by appropriate scientific data and rationale.

All scientific publications used in lieu of, or to supplement, product-specific data should be critically appraised to ensure their relevance to the data requirements for the product to be registered or varied. A reliable scientific reference is one that demonstrates relevance, methodological rigour, robust statistical analysis, plausible and consistent results, and transparent reporting, including limitations.

Applicants should transparently address all relevant literature, including evidence that may adversely impact the application, and clearly identify any limitations or uncertainties. The applicant should demonstrate how the totality of evidence supports the proposed conclusions.

For example, where a proposed dose is justified based on published literature, any evidence indicating that the dose may be suboptimal or inadequate should also be acknowledged. Applicants are expected to provide a reasoned justification for the selected dose, taking into account both supportive and conflicting evidence.

Title page

A title page should include the following information and other identifying information as appropriate:

Applicant	
Submission category	<Registration application> <Variation application>
Product name	
Active constituent(s) and concentration	

1. Introduction

Include and identify the type of submission e.g. new product registration, variation, technical assessment only, etc. and any other information that could clarify the context of the application. The following information is expected for a new product submission. For variations, elements of the following can be included where relevant to assist assessment.

Provide a short summary describing the product, its active constituent(s) and concentration(s), the formulation type and proposed use of product.

Example: Product Y is an oral solution containing [amount] [units] [active constituent name] and is indicated for the control / treatment / management of X in dogs.

State whether your product contains new or existing active constituents and any other information that may be relevant.

Example: [active constituent name] is approved by the APVMA for topical use in both dogs and cats. The proposed product represents the first administration of [active constituent name] in dogs as an oral solution.

Describe the target population or species, and specify the disease, condition, or indication for the proposed product. Types of information that may be relevant here include:

- Clear identification and description of the abnormal condition affecting the animal.
- Etiology (primary cause, risk factors and contributing factors).
- Pathogenesis (mechanism e.g how the disease alters normal body functions).
- Clinical features (symptoms and signs) and linkage to primary / secondary efficacy assessment parameters.
- Epidemiology (incidence, prevalence and demographic distribution).
- Treatment and Management.

  If targeting parasites this information could include:

  – The nature and severity of damage/harm to the animal.
  – Relevant aspects of the parasite(s) biology (e.g. life cycle) and its interaction with the animal.
  – Information on commercially acceptable levels of control, including economic thresholds, for each parasite claim.

Provide a summary of pharmacology of product- how the active constituent(s) in the product works to achieve the desired effect.

Provide a description of the use pattern— dosage, route(s) of administration, dosage schedule.

Provide formulation details explaining any different names applied during development.

Identify applicable APVMA and /or international guidelines used in the generation of the submitted data, including relevant guidelines you may have deviated from.

Table 1: Simplified table of proposed use pattern

	What is being proposed	Current (if applicable – example: for extension)
Target animal		
Indication		
Route of administration		
Dosage regime		
Changes to use pattern	Include comments on any specific aspects of proposed use that are novel or at variance with similar compounds or common use pattern	

2. Efficacy data summary

Provide a summary of all efficacy studies in the target species.

Summarise the studies submitted as well as provide **a clear link between the study results and the proposed label statements**. A summary table such as that shown below in Table 2, is an effective way of demonstrating whether sufficient studies covering the APVMA data requirements for the registration of a veterinary pharmaceutical product have been provided to justify the proposed claims and label statements. Where a large number of studies are being submitted, it may be more helpful to provide a summary table for each following section (i.e. Dose determination, Dose confirmation, Confirmatory clinical/field studies) rather than a single summary table.

Table 2: Provide an overview of studies performed in the target species that support the label claims

Indication	Type of Study/Species/Location	Appendix/ Reference	Formulation Used Developmental/Final	Key Efficacy Outcomes and claim language supported
For the control of fleas (Ctenocephalides felis)	Dose confirmation C. felis (US strain)	8.21	Final formulation	≥99.7% efficacy throughout the study. Supports a claim for control of fleas
	Field study C. felis (uniform rainfall, Australia)	8.22	Final formulation	≥95.9% efficacy at all assessments in a subtropical environment with uniform rainfall.

Indication	Type of Study/Species/Location	Appendix/ Reference	Formulation Used Developmental/Final	Key Efficacy Outcomes and claim language supported
				Supports a claim for control of fleas
	Field study C. felis(summer dominant rainfall, Australia)	8.23	Final formulation	≥97.1% efficacy at all assessments in a subtropical environment with summer-dominant rainfall. Supports a claim for control of fleas
For the prevention of heartworm (Dirofilaria immitis) infection.	Dose confirmation D. immitis (US)	8.12	Final formulation	100% efficacy at all post-treatment assessments.
	Dose confirmation D. immitis (US)	8.13	Final formulation	100% efficacy at all post-treatment assessments
For the Reduction of pain and inflammation associated with osteoarthritis in dogs	Pivotal pharmacokinetic study in dogs	8.28	Final Formulation	Demonstrated that XX administered orally to dogs is readily absorbed (Tmax of 2-4 h) with high bioavailability (80%), and a long terminal half-life (t1/2 36-40 h). Supports the proposed route of administration and dosing regimen
	Dose determination study	8.29	Developmental	Higher dose rates of XX (at X1 and X2) had better efficacy than the lowest dose rate used (X 0.5). However, efficacy between the x1 and x2 dose rates was not significantly different hence the x1 dose rate

Indication	Type of Study/Species/Location	Appendix/ Reference	Formulation Used Developmental/Final	Key Efficacy Outcomes and claim language supported
				was selected as the optimal dose
	Field dose confirmation study	8.30	Final Formulation	There was significantly higher treatment success rate in the treatment group (87.5%, P=0.0110), compared to the control group (23.1%). Supports that a weekly oral dose of 4mg/kg reduces the signs of lameness and pain in dogs with osteoarthritis.
	Multicentre placebo controlled clinical efficacy study	8.31	Final Formulation	Clinical efficacy of Product X administered to dogs with osteoarthritis at a weekly maintenance dose of 5 mg/kg and that of Product Y (positive control) were statistically superior to placebo. The efficacy of Product X in dogs with osteoarthritis was non-inferior to the positive control. Product X had a good safety profile characterised by a low incidence of gastrointestinal disturbances.
An aid in the treatment of anxiety disorders in dogs such as excessive	Pharmacokinetics in dogs	8.5	Not applicable	Scientific literature and nomination of reference products are presented for the active which has

Indication	Type of Study/Species/Location	Appendix/ Reference	Formulation Used Developmental/Final	Key Efficacy Outcomes and claim language supported
grooming and tail chasing				been widely used and studied in dogs for over a decade
	Dose determination/confirmation study	8.6	Final formulation	Biowaiver and dissolution data is provided. The active substance is a BCS class I, at the same concentration as the reference product and there are no excipients affecting bioavailability. The pH dissolution study demonstrated the proposed product is the same as the registered reference product.

Studies undertaken using different formulations (e.g. former formulations, unregistered formulations or formulations from overseas) considered to be supportive of the proposed product should also be included in the table above. Product codes and full formulation details should be provided in an Appendix to the overview document (or separate document as appropriate). A scientific argument justifying the inclusion of trials using other formulations is required and could include a side-by-side comparison of the formulations including % change in excipients where appropriate.

Where overseas studies are submitted in support of an application, applicants should provide a clear justification for the applicability and relevance of the overseas efficacy and safety data to Australian conditions. This justification should address, as applicable, key environmental factors such as pathogen species and strains, geographical regions, climatic conditions, production systems and animal husbandry practices.

Where gaps appear to exist, these can be highlighted in the in the relevant section below and scientific argument provided.

A map with trial location(s) is recommended, where applicable e.g. for parasiticide registration applications where study regions requirements are specified.

2.1 Pharmacological data

2.1.1 Pharmacodynamics

Begin with a summary statement on the number of studies investigating the pharmacodynamics of the active constituent(s) in the proposed product.

Example: A total of X in vitro and Y in vivo studies were conducted to characterise the pharmacodynamic effects of the active moiety and active metabolite.

Summarise each study including details on the methodology, assessment parameters and results (see example below). Types of studies/data under this section include:

- Mechanism of action studies
- Effect in *in vivo* model studies
- Pharmacological effects

Alternatively, published literature may be used to support the pharmacological profile of the proposed product. In such cases, each reference should be summarised, with emphasis on the methodologies applied, the assessment parameters evaluated, and the results obtained, including their relevance to the proposed product.

Example: Study xxx-xxx-xx or Gonzalez et al. (2014) evaluated the pharmacological activity of oclacitinib, a Janus kinase (JAK) inhibitor. Using isolated enzyme assays and in vitro human and canine cell-based models, the potency and selectivity of oclacitinib were assessed against JAK family members and cytokines that signal via JAK pathways.

Oclacitinib inhibited JAK family members with IC_{50} values of 10–99 nM, with greatest potency against JAK1 (IC_{50} = 10 nM), and showed no significant activity against 38 non-JAK kinases (IC_{50} > 1000 nM). In cell-based assays, it inhibited JAK1-dependent cytokines associated with allergy, inflammation, and pruritus (IL-2, IL-4, IL-6, IL-13, IL-31; IC_{50} 36–249 nM), with minimal effects on non-JAK1-dependent cytokines (IC_{50} > 1000 nM).

These findings demonstrate selective inhibition of JAK1-mediated cytokine signalling, supporting the proposed mechanism of action in controlling allergic skin disease in dogs.

At the end of the section provide conclusions on pharmacodynamics of the product and propose statements for the label based on pharmacological data.

2.1.2 Pharmacokinetics

Begin with a summary statement on the number of trials investigating the pharmacokinetics of the product that have been submitted.

Example: The absorption, metabolism, distribution and excretion (ADME) of Active X (and related molecules) have been studied in various species, including dogs. A total of x studies was conducted in dogs to investigate the pharmacokinetics of the product. Y studies conducted in non-target species are also included in this submission as supportive information.

Summarise each study including details on the methodology, assessment parameters and results. Types of studies/data under this section may include:

- Absorption and exposure studies/data
- Distribution studies/data
- Elimination studies/data
- Metabolism studies/data
- Excretion studies/data
- Potential for pharmacokinetic interactions
- Single dose pharmacokinetic studies in the target species
- Repeated dose pharmacokinetic studies in the target species
- Toxicokinetics

Alternatively, published literature may be used to support the pharmacokinetic profile of the proposed product. In such cases, each reference should be summarised, with emphasis on the methodologies applied, the assessment parameters evaluated, and the results obtained, including their relevance to the proposed product.

At the end of the section provide conclusions on the pharmacokinetics of the product and propose statements for the label based on pharmacokinetics.

Example: The following pharmacokinetic label statement is proposed.

Peak plasma concentrations of <active> are attained within 2 hours in fasting and fed situations. <Active> is predominantly eliminated rapidly, although a secondary prolonged terminal elimination phase is also observed. Excretion of <active> occurs primarily via the urinary route in dogs. Following repeated administration of <product>, slight accumulation of <active> in plasma is observed, with steady-state concentrations attained within approximately 6 days.

2.2 Dose determination studies

Begin with a summary statement on the number of studies investigating the optimum dose of the proposed product. Describe the rationale for selection of the dose and administration schedule.

Example: X dose determination studies were conducted in dogs/sheep to determine the effective dose of the product for the treatment of xx disease or control of parasite infestation.

Provide summaries of studies focusing on:

- Methods
- Results
- Conclusions

Example: A GLP and GCP-compliant dose determination study (ES-DD-113) was conducted to establish the minimum efficacious dose of fipronil against Rhipicephalus sanguineus (brown dog tick) in dogs. 50 dogs demonstrating suitable host–parasite susceptibility (≥25% live tick attachment) were randomly allocated to 5 treatment groups and infested with 50 adult ticks prior to treatment. On Day 0, dogs received either a mock treatment or fipronil at target dose rates of approximately 20, 30, 40, or 50 mg/kg body weight. Efficacy was assessed 48 hours after treatment and following weekly reinfestations from Day 21 to Day 63.

The primary efficacy endpoint was the reduction in live and live attached ticks relative to the mock-treated control group. Adequate infestations were achieved throughout the study. All fipronil-treated groups demonstrated significantly lower tick counts than controls at all assessment time points ($p \leq 0.001$). Based on both arithmetic and geometric mean analyses, the minimum efficacious dose rate was determined to be 20 mg/kg, providing effective control of R. sanguineus for at least one month and up to 6 weeks post-treatment.

The efficacy results are shown in Table 1.

Table 1 Dose determination, *Rhipicephalus sanguineus*
Day of tick count, adequacy of infestation, arithmetic mean counts of R. sanguineus on mock-treated and drug-treated dogs and effectiveness (%), **efficacy bolded**.

	Day 2	Day 23	Day 30	Day 37	Day 44	Day 51	Day 58	Day 65
Dogs with ≥ 25% live attachment	10/10	10/10	10/10	9/10	10/10	10/10	10/10	10/10
Mean live attachment	69%	43%	59%	48%	61%	52%	51%	55%
0 mg/kg	34.5	21.9	29.4	24.3	30.6	26.1	25.6	27.4
20 mg/kg	0, 100%	0.1, **99%**	0.0, **100%**	0.0, **100%**	1.0, **97%**	1.9, **93%**	3.0, 88%	5.6, 80%
30 mg/kg	0, 100%	0.1, **99%**	1.1, **96%**	0.1, **99.5%**	1.1, **96%**	1.1, **96%**	2.1, **92%**	4.9, 82%
40 mg/kg	0.1, 99%	0.5, 98%	0.1, **99.6%**	0.5, 98%	0.4, 99%	0.4, 99%	0.5, 98%	2.6, **90.4%**
50 mg/kg	0, 100%	0.1, **99%**	0.0, **100%**	0.3, **99%**	1.9, **93%**	2.0, **92%**	3.0, 88%	6.3, 77%

In addition, blood samples were collected prior to dosing and at 9 time points post dosing to determine fipronil concentrations. Haematology and clinical chemistry parameters were assessed once before and once after dosing. Pharmacokinetic evaluation showed no statistically significant ($p > 0.36$) differences between dose groups or between sexes for half-life, mean residence time, dose-normalised maximum concentrations, or area under the concentration-time curve (AUC). No significant dose-related trends were identified.

The treatment was well tolerated. Clinical observations were limited to sporadic skin alterations, diarrhoea, and weight loss, with no serious adverse events reported. Investigators considered these findings unlikely to be treatment related. No significant differences in body weight changes were observed between groups ($p > 0.31$), and no clinically relevant haematological or clinical chemistry abnormalities were detected.

The study was conducted largely in accordance with WAAVP (2013) guidelines. Although traditional dose-ranging increments were not used, the selected dose levels provided a more precise determination of the minimum efficacious dose, supported by results from earlier development studies.

Overall, the findings from this study, together with pharmacokinetic modelling, support a recommended minimum dose rate of 20 mg fipronil/kg body weight for a globally marketed product intended to provide efficacy against both endemic and non-endemic R. sanguineus populations.

At the end of the section provide conclusions on dose selection and point out the related label statements.

Example: Higher treatment success rates in terms of both primary and secondary variables of efficacy were observed with the higher dose rates, with the proposed product dose of 20 mg Active /kg BW reaching statistical significance from the control treatment but not with the highest dose rate, suggesting that it was more effective than the lower dose rates but no worse than the highest dose rate. **This dose was therefore chosen for further development.**

2.3 Dose confirmation studies

Begin with a summary statement on the number of trials conducted to confirm the optimum dose of the proposed product.

Example 1: A total of 2 dose confirmation studies was conducted to confirm the dose of Product Y for the for the control of osteoarthritic pain. The animals used in the studies were confirmed as having mild to severe osteoarthritis and the final formulation was used in all studies. All studies were conducted overseas.

Example 2: Three (3) dose confirmation studies were conducted to confirm the dose of Product Y for the for control of the brown dog tick. One pivotal dose confirmation study was conducted using the final product formulation with Australian strains of *Rhipicephalus sanguineus*. A further one US and one EU dose confirmation studies were conducted with the final product formulation against Rhipicephalus sanguineus strains from the respective regions.

Provide summaries of studies focusing on:

- Methods
- Results
- Conclusions

At the end of the section provide conclusions from the dose confirmation studies and propose related label statements.

Example: The dose confirmation studies demonstrated that treatment with Product Y administered orally once a day at 5 mg /kg BW in dogs with osteoarthritis resulted in high treatment success rates in terms of both primary and secondary variables of efficacy and reached statistical significance from the CP treatment. There was a clear reduction in inflammation and lameness associated with osteoarthritis in the treated dogs. Additionally, the studies highlighted the rapid onset of efficacy of Product Y with significant improvement of inflammation seen after the first

dose and sustained throughout the studies. Therefore, IVP daily dosing at 5 mg Active /kg BW was confirmed as final dosing regimen.

2.4 Confirmatory clinical/field studies

Begin with a summary statement on the number of trials conducted to confirm the efficacy and safety of the proposed product under field conditions.

Example: Four field studies were conducted within Australia and overseas to evaluate efficacy and safety of once daily oral administration of Product Y for the treatment of clinical manifestations of atopic dermatitis in client-owned dogs. The first and second studies were in support of the claim for the treatment of pruritus associated with atopic dermatitis. The second and third studies were in support of the claim for treatment of clinical manifestations of Atopic Dermatitis. All studies were conducted with the final formulation. These are summarised below.

Provide summaries of individual studies focusing on:

- Methods
- Results
- Product usability
- Conclusions

At the end of the section provide conclusions from the field efficacy studies and propose the related label statements.

Example: The results of the efficacy field studies confirm the label claim as the product was successful in the reducing pruritus and clinical symptoms associated with atopic dermatitis in dogs when administered once daily at a dose of 5 mg Active/kg BW.

Also, in these studies, diverse population of dogs with atopic dermatitis were used which included various breeds and ages, thus, accurately reflecting the target field population.

2.5 Palatability/acceptability studies

Depending on the nature, dose form and use pattern of an orally administered product, its palatability may directly influence the amount ingested by an animal and therefore may directly affect dosage and efficacy.

Begin with a summary statement on the number of studies conducted to confirm the palatability/acceptability of the proposed product.

Provide summaries of individual studies focusing on:

- Methods
- Results
- Conclusions

At the end of the section provide conclusions from the palatability/acceptability studies and propose the related label statements.

2.6 Overall conclusions on efficacy

Write a summary and conclusion on the entire chapter focusing on the level and consistency of efficacy demonstrated in studies and how it supports the level of claim sought and or meets the APVMA data requirements. Where inconsistent or lower than expected levels of efficacy are observed in the study data, these must be discussed including implications or impact on animal safety, welfare and production.

Discuss any efficacy data limitations.

Confirm appropriate label instructions to communicate a specific use pattern and manage user expectations and promote optimal animal health outcomes.

3. Target animal safety data

3.1 Safety data summary

Provide a summary statement on the number of trials conducted to confirm the safety of the proposed product in the target species. The summary can also point out if there any target animal safety studies that are typically required for the proposed product that have not been provided.

Example: Five (5) preclinical safety pharmacology studies, one maximum tolerated dose study and one pivotal GLP-compliant target animal safety study were conducted to determine the target animal safety of the proposed product. In addition, safety data obtained from 3 non-pivotal margin of safety studies, 6 efficacy clinical trials and published literature references is also presented. No reproductive safety studies have been included in this submission.

3.2 Preclinical studies

Provide a summary of the *in vitro* and *in vivo* preclinical safety studies performed to establish the toxicity profile of the active constituent and product. Provide summaries of individual studies focusing on:

- Methods
- Results
- Conclusions

At the end of the section provide conclusions from the preclinical safety studies and point out the related label statements.

3.3 Non-pivotal margin of safety studies

Describe any non-pivotal safety studies including single and multiple dose safety studies conducted to establish the safety of the proposed dose and duration of treatment. Provide summaries of individual studies focusing on:

- Methods
- Results
- Conclusions

At the end of the section provide conclusions and recommendations from the non-pivotal studies.

3.4 Pivotal margin of safety study

Provide details of the pivotal target animal safety study conducted in the target species focusing on:

- Methods

- Results
- Conclusions

Types of studies/data under this section include ‘dose rate’ and ‘duration of treatment’ studies.

At the end of the section provide conclusions on the margin of safety of the proposed product and propose the related label statements including adverse events/side effects distribution and frequency.

3.5 Safety evaluation of product in clinical/field studies

Clinical/field studies often incorporate both evaluation of efficacy and target animal safety components. In such instances, there is no need to repeat the full study details. Rather you can provide only summaries of the target animal safety components including the distribution and frequency of observed adverse events and their classifications.

Example: Study xxx-xxx-xx investigated the efficacy and safety of the proposed product under user conditions. The product was administered to 256 dogs of varying ages and breeds in accordance with the proposed label dose and directions for use. Safety was evaluated through adverse event reporting. 114 AEs were reported in 88 dogs, comprising 49 in the treatment group, 46 in the positive control group, and 19 in the placebo group. Causality assessment classified 56% of AEs as unlikely, 18% as possible, 10% as unknown, and 16% as probable. Severity classification across all groups indicated that 67% of AEs were mild, 24% moderate, 3% life-threatening, and 6% severe. Most AEs assessed as possibly or probably treatment-related were mild to moderate in severity, predominantly gastrointestinal in nature (diarrhoea and vomiting), were distributed across the treatment and positive control groups, and all resolved without sequelae.

The second field efficacy study, study xxx-xxx-xx, also evaluated the safety of the proposed product under user conditions. A total of 52 AEs were reported in 37 dogs, including 28 in the treatment group, 23 in the positive control group, and 1 in the placebo group. Causality assessment classified 40% of AEs as unlikely, 27% as possible, 21% as unknown, and 12% as probable. Across treatment groups, 65% of AEs were mild, 21% moderate, 10% life-threatening, and 4% severe. Five (5) severe or life-threatening AEs were considered possibly or probably treatment-related, occurring in 2 animals (one in the treatment group and one in the positive control group). Consistent with the first study, most AEs assessed as possibly or probably related to treatment were mild to moderate, predominantly gastrointestinal (e.g. diarrhoea and vomiting), occurred in both the investigational veterinary product and positive control groups, and resolved completely.

Conclude the section by summarising the target animal safety findings from the field efficacy and safety studies and propose appropriate label statements based on the observed field safety outcomes.

Example: The product was well tolerated and most common adverse events reported were diarrhoea and emesis. These have been included within the proposed label.

3.6 Reproductive toxicity/reproductive safety studies

Make a statement regarding the availability (or otherwise) of results from studies that evaluated the impact of the proposed product (or active) on reproductive function of the target species.

Provide details of the reproductive toxicity/ reproductive function studies conducted in the target species focusing on:

- Methods
- Results
- Conclusions

The studies may include safety studies in breeding, pregnant and lactating animals.

At the end of the section provide conclusions on the reproductive safety of the proposed product and propose the related label statements. If data from reproductive function studies are not available, you should propose a standard precautionary statement for inclusion on the label.

3.7 Compatibility studies

Discuss interactions with other veterinary medical products and provide details of clinical studies that demonstrate the compatibility of the proposed product with routine prophylactic treatments if relevant or with specified products if seeking compatibility claims.

Propose statements for the label based on the information on interactions and compatibility studies.

3.8 Pharmacovigilance

Make a statement regarding the availability of pharmacovigilance data from overseas registrations. Discuss whether post-market surveillance has identified adverse events not observed during clinical trials or circumstances under which the product should be used with caution.

Propose statements for the label based on this data.

3.9 Overall conclusions on target animal safety

Write a summary and conclusion on the entire chapter focusing on the level and consistency of safety demonstrated in studies and how it supports the proposed use pattern and or meets the APVMA data requirements. Where inconsistent or risks to safety are observed in the study data, these must be discussed including implications or impact on animal safety, and welfare.

Discuss any safety data limitations.

Confirm appropriate label statements required to ensure target animal safety.

4. Related and other studies or data

Provide details of any other studies being provided to support the efficacy and safety of the proposed product. A brief description of the type of study and how it was conducted plus results presented is appropriate. Types of studies/data under this section include:

- In vivo or in vitro bioequivalence studies
- Clinical case studies
- Topical studies, inhalation studies, tissue irritation studies
- Minimum inhibitory concentration studies
- Effects on Taste or Produce (Organoleptic Effects)
- Effects on Hides and Fleeces
- Accidental Administration or Exposure to Non-Target Animals

Provide any evidence of possible adverse effects from accidental administration to or exposure of animals other than those for which the product is recommended. If no significant effects were observed or are expected, a summary of the rationale and a conclusion are sufficient. In case significant effects were observed, a more detailed presentation of data is required.

Propose warning statements for inclusion in the product label if relevant.