Final report

Colere Consultancy: Goat Pain Relief- Phase 2

Project code: B.GOA.2402

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Abstract

The use of pain relief products is now a critical part of animal welfare and red meat productivity. Research has clearly demonstrated that using these products decreases animal stress, elevates weight loss related to husbandry practices and reduces animal handling costs. In addition, the widescale adoption of these products has helped the Australian red meat industry maintain social licence in an increasingly complex market. Unfortunately, minor animal production sectors such as goats have yet to gain access to these products due to a combination of market size and the complexity of registration in new species.

Colere Group have been closely involved with the management of the process to deliver pain relief options to the Australian goat industry for over two years. The work has been supported by Animal Health Australia (AHA), the Goat Industry Council of Australia (GICA) and Meat and Livestock Australia (MLA). This began with the investigation of pain medication actives and options, and evaluation of what is needed by each of the goat industry sectors. Meloxicam as a buccal application was selected as the best option for industry to pursue, given its analgesic properties, cost effectiveness, ease of use, existing research and the willingness of the formulation owners to partner with industry.

This consultancy was to support the ongoing discussions with a commercial company, continue to build the regulatory package and develop the work program needed to fill the data gaps required for APVMA registration of their “over the counter” meloxicam-based product, for goats.

As part of the project an industry workshop was held which was attended by APVMA and industry stakeholders. This was able to present much of the challenges relating to the registration of products in minor production species as well as the specific complications relating to pain.

This report outlines the non-confidential aspects of progress to date on the whole project, and in particular presents the potential pathway through to a registered product being made available to goat producers in Australia.

Executive summary

Background

Colere Group is working behalf of Meat and Livestock Australia (MLA), Animal Health Australia (AHA) and the Goat Industry Council of Australia (GICA) to improve access of the goat industry to pain relief products for use in everyday animal husbandry procedures, in line with contemporary societal expectations of animal welfare for farmed animals.

The use of pain relief is increasingly a central part of both animal welfare and productivity. Availability of registered OTC products in cattle and sheep has resulted in significant uptake in these industries over the last decade and since the PETA action of the early 2000s. Unfortunately, there are currently no products available to minor animal industries such as goats, outside of off-label prescription by vets. A survey of vets and goat producers indicates that a lack of access to vets- particularly those with relevant minor species animal experience- and absence of registered products has significantly hindered the use of pain medications in species such as goats. This is putting at risk the industry's social license and reputation.

At the end of the previous project (B.GOA.2401) Colere Group had (with industry support):

1. Successfully presented to the federal Department of Agriculture Fisheries and Forestry- Agvet Chemical Minor Use Prioritisation Forum (Agvet Forum) to receive a grant of $350,000 to support the process of registration.
2. Undertaken an overview of the nine main modules with the data/information required for development of a regulatory package.
3. Through industry survey and consultation, a clear understanding of producer needs and the support for a product, when made available.
4. Strong support from our commercial partner and a commitment to provide technical and (potentially) financial support.

What is the role of this project?

Before committing to the major investment in the trial program, there is specific clarification required from the APVMA around trial number and types. Rather than either just progress with their previous recommendations, which were primarily generic in nature, or force them into a position whereby they reiterate these previous recommendations, we believe utilising some collaborative industry consultation and feedback might provide reasoning to reduce the scope and scale of what they have suggested, given the unique nature of this problem, and the shared responsibility for solution finding, between producers, industry and government.

This short consultancy was designed to maintain the industry impetus in the current collaboration and bridge the gap through to the initiation of the R&D investment that will deliver the required studies. It organised the collaborative consultation and then built a PAA submission, based on learnings and guidance.

Results/key findings

The past six months have provided significant clarification as to the complexity, cost and methodology for developing a comprehensive regulatory package that would successfully allow Australian goat producers to have access to an "over the counter" pain relief product for their animals. Major breakthroughs include:

- Strengthening of the collaborative partnership with our commercial partner was a critical outcome required to progress this project and a visit from Colere Group and GICA enabled us to present our progress to date as well as the potential commercial opportunity. It was as a result of this meeting that they have committed to supporting the program.
- Improved potential position in relation to the number and scope of studies required for a registration.
- While not yet confirmed, efficacy may be a lower risk/issue than previously envisaged. All levels of pain relief is a positive outcome and pain is ubiquitous (regardless of cause), meaning there may be scope for a more extensive label.
- We need to approach our Pre-application assistance consultation (PAA) with some of our own data (e.g. from an animal study) plus everything else we have written up and correlated if we want the best possible outcome and a reduced trial burden.

Benefits to industry

While access to pain relief products is a high priority for the industry, there is a clear understanding that the path and process to gain this access through APVMA registration of a pain product is complex and costs difficult to define. The project was designed to seek clarity in process and cost, before further commitment is made by industry. It is likely that this project will be one of the largest ever undertaken by this industry, and all effort needs to be made to maximise leverage and reduce unnecessary expenditure.

Next steps and recommendations

The following next steps are recommended to MLA and the industry:

1. **Provide a response to APVMA's NSAID Draft Guideline**
    - This is critical for this project and indeed for future registrations of NSAID products in the red meat industry. There is a very real concern that the current guidelines create an unachievable target for efficacy studies and completely miss the point that pain management at any level is useful. Colere can develop a response in collaboration with CSIRO for submission in January. (Consultation period ends 20 Jan 2025).
2. **Progress preliminary studies**
    - Continue discussion with researchers about undertaking an animal, able to generate a data bridge between their existing and in-progress work using oral meloxicam.
3. **New Pre-application assistance consultation (PAA)**

- We have recommended we undertake a PAA, with an opportunity to define future studies and therefore costs, if the technical PAA submission is sufficient and the husbandry need is clear.

4. Negotiate Commercial Partnership

- An agreement will need to be made directly between MLA and our commercial partner that spells out both the short-term obligations from parties as well as the form and value of future royalty arrangements.

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1. Background

How we got here

The lack of access to pain relief products for the Australian goat industries is a clear and present reputational risk that could at any time develop into a significant issue. Across the animal production sectors there is an understanding that best practice methodology for minor/regular husbandry operations (e.g. castration, disbudding) includes the use of pain relief medication. While there is an understanding in technical circles that the size of the industry and costs of registration often lead to a lack of registrations in agricultural production, this is not an acceptable excuse with a highly sensitised public.

In previous investment by the industry (GICA, AHA and MLA), Colere Group were contracted to undertake a thorough investigation of the pain medication field and the needs and potential uses cases of the Australian goat industry sectors. ("***Pain Relief options for the Australian Goat Industry Technical Report***").

The following findings and recommendations were provided to the industry:

Previous Report Findings

1. The husbandry practices that represent the greatest external reputational risk for the goat industry, is a low-risk practice for meat or milk residues when considering the use of a range of potential actives.
2. Equitable access to pain relief is currently front and centre for regulators and industry, meaning we need to present a plan for how the goat industry and animal health product manufacturers are going to work together to address those challenges.
3. There are no approved label claims for pain medications for goats registered in the EU or USA, and only one or two medications registered globally. This indicates the huge needs gap the industry faces locally and globally as well as the potential market.
4. The goat industry needs to be prepared to demonstrate it is committed to investing in the studies required to apply for an extension of label claim and use instructions.
5. The most critical of the next steps will be the outcome of discussions with animal health companies, which will inform the best/first choice of product for further investigation/investment.
6. This project schedule is an industry plan for access to pain relief products that includes development study schedules and timelines that will result in a new registration application(s) that extends the label claims our targeted product.

The final report for this project was presented to the industry in May of 2023, and presented a clear case for the industry to invest in this next stage.

Engagement with industry and Animal Health companies

Following the presentation of the report findings to MLA, AHA and GICA it was agreed to:

- Undertake a broad industry consultation and survey to understand the needs and challenges faced by producers and vets.
- Initially focus on an "over the counter" version of meloxicam.
- The goal is to achieve a full registration, to avoid the need to regularly support renewal of an industry permit, however if the burden of proof required was too high then a permit would be better than nothing.

At the end of the previous project Colere Group had (with industry support):

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What is the role of this project?

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Objectives

- *Provide the cohesion between the key stakeholders through regular managed meetings and communications.* Regular online meetings were held, visits were made to industry partners, commercial partners and research collaborators.

- *Lead industry and government representation in meeting with regulators to discuss the need for pain management in the industry, presenting the challenges of producers accessing utilising products, and highlighting the risks to industry and trade if they can't.* A broad industry workshop was held in Canberra on the 26th November to bring together parties to discuss the issue of access to pain relief for minor production species.

- *Continue to unpack the available data and build written arguments (reducing the need for additional studies). This aims to maximise the use of previous data.* Contact made with research groups globally and new argument made resulting from the workshop discussions.

- *Consult with providers of contract research to enable costings of the total project costs to be presented to MLA and GICA. This may also include seeking overseas providers.* Basic costs for key studies and potential for leverage and collaboration found.

- *Assist MLA, GICA and AHA in the development of a costed project to manage and deliver the regulatory package for the registration for use in goats. In practical terms, this means confirming with APVMA the required data set and identifying the work program and third-party data required to fulfill these needs.* A new work program was developed and will be presented as part of a PAA in 2025.

2. Results

2.1 Commercial partner/product

In the previous project, the decision was made to select the non-steroidal, anti-inflammatory meloxicam as our active of choice. The key reasons included:

- **Ease of use**- doses are based on weight and easily administered orally to animals of all sizes.
- **Well known product**- The product has been in the market for many years and is known to have a low risk profile and good success rate. Vets and producers provided positive feedback on use and effectiveness.
- **Product flexibility**- Meloxicam can be used for all pain relief situations as it is systemically active, and targets the site of pain, rather than needing to be applied to a site directly. This particularly suits producers undertaking multiple husbandry practices in one day.

The value of having these longer, face-to-face meetings was quickly made evident following our presentation of progress and industry plans. Since these meetings they have communicated the following:

- The product use for goats in Australia is potentially larger than they had anticipated, especially when considering the strong industry support for an OTC product (as per survey), the number of goats in productive care (i.e. outside of rangeland) and the potential use pattern (volume and doses utilised per animal).
- The opportunity in the wider global market, based in part on the regulatory package we will be developing, is significant and we have shown them the demand.
- Based on discussions, they have increased their technical support and have also considered financial support for the project.

Colere Group recommends that a commercial agreement is negotiated in early 2025, to lock in the promised support and provide a strong incentive for them to continue to help our team.

2.2 Results from Workshop

The workshop was held on November 26th, 2024, and was designed to bring together all relevant parties and stakeholders from across government and industry to discuss access to pain relief in minor species, project progress and identify challenges. The expansion of the title beyond goats was a purposeful approach to bring in the support of industries such as deer, alpaca, camel and buffalo, who have similar challenges when it comes to access to animal health products.

Some of the key workshop presentations and discussion from the workshop:

An experienced industry goat veterinarian discussed her experience using and dispensing meloxicam as a practicing goat medicine expert, including:

- The difficulties of prescribing pain relief off-label: State legislative requirements for vets to visit the farm, difficulties of distance, reluctance for some producers to consult with vets due to costs.
- The risk to vets of recommending off-label dose and WHP without access to data. This may also influence non-experienced vets reduced willingness to prescribe.
- The paucity of vets with sufficient expertise in goats, alpaca and other minor species.
- A need for access to pain relief products for immediate use (i.e. kept on farm). While a Tele-vet off-label prescription might be possible, the ability to then get to the closest outlet can also be challenging for more remote producers to buy the actual product.
- Small product volumes are also critical to drive use in small producers due to the cost.

A livestock welfare scientist discussed broadly the physiological response of pain in grazing animals, and how NSAIDs and other pain relief products work in response to a tissue insult. She made the following points:

- The aim of pain relief is return to function. Additionally noting that complete relief of pain may not be advantageous because it could lead to loss of protective behaviours and potentially worsen the initial insult.
- Although there are multiple causes for pain, sites of insult and degrees of tissue damage, there is essentially only one pain pathway. In theory therefore an effective therapeutic need not necessarily be tested for all possible causes and sites of pain.
- It is difficult to evaluate perception of pain in stoic animals. Behavioural evaluation remains the most reliable method. Physiological responses maybe confounded by the stress of the study handling so are not reliable by themselves. Similarly, serological measures are frequently impacted by the stress induced by the study handling.
  For these reasons of complexity and high labour costs, behavioural based pain studies are expensive to run.

An overview of development of the APVMA's NSAID Draft Guideline and insight into the consultation process was provided for this GL (technical guideline). The GL was developed with scientific input and with consideration of the CVMP and CVM guidance documents. Guidelines are intended to provide guidance to APVMA evaluators, they are not requirements.

- Given the consultation process for this GL from APVMA is still open, there is still an opportunity for representatives from industry to provide feedback.

2.2.1 Takeaways from the workshop

- There was broad and universal agreement that minor production industries need access to pain relief products (along with other animal health products) to maintain their social license and productivity competitiveness.

- The other minor industries are aware of the challenges of getting access to pain relief products, but this has yet to rate highly in their priority of needs.
- Pain is technically very different to other management goals when it comes to efficacy targets and metrics. It can be difficult to accurately quantify and even lower levels of pain relief should be considered useful.

Colere Group recommends that a submission to APVMA is made in response to their NSAID Draft Guideline, and that this submission should be an independent, science driven response.

The APVMA will consider and then provide a response summarising the data they then will require. The APVMA advised the approach of a single PAA submission, and single response, and cautioned against returning repeatedly for advice, as their advice may change over time.

2.3 Investigation/Analysis of literature and data

The following section relates to the research undertaken to clarify and consider each of the regulatory modules to better understand the path and process of trials and arguments required.

Efficacy Studies

How pain can be detected in small ruminants:
Pain detection and evaluation in goats is difficult. Small ruminants have evolved to not overtly display pain to avoid predation, so pain detection is more difficult than larger ruminants (cattle).
Behaviour is the most reliable measurable for pain response, while still acknowledging that measuring behaviours generally found to be associated with pain is not the same as measuring the pain itself.

- Alison Small's team have previously developed a pain response matrix combining mobility, posture and behaviour (composite pain scale), allocating a 'traffic light' system of red/pain, orange/possibly pain and green/ no pain, which enables clearer efficacy evaluation to obtain P values.
- This work development was co-funded by MLA. She also wrote a report for AWI 2020: Gap evaluation Pain alleviation in sheep. The matrix system was used in efficacy studies for Buccalgesic in sheep, to support APVMA registration.
- Facial grimace scale: There are facial grimace scales developed in a few animals, such as cattle, cats, mice, but they haven't yet been validated in sheep or goats. Generally in cattle and other animals, the grimace occurs in immediate response to the painful stimuli but after a short time it may lessen, meaning that such an evaluation system may be a useful measure for local anaesthesia efficacy but not for NSAIDs given their 20 minutes effect time.
- Vocalisation: unreliable.
- Accelerators (measuring mobility): may work well for lameness model.

Physical:

- Physiological changes such as heart rate, respiratory rate blood pressure etc: These are easy to do at same time as blood sampling but the animals may be responding to the stress of handling so the data may be confounded.
- Infrared thermography of eye (eye temperature): Both CSIRO and Kansas State have used this previously. They both report that it may be difficult to obtain clean data set. It is important to undertaken to a rigorous protocol, need to restrain head in specific way to enable correct eye

imaging, although once procedures in place it can be straightforward to measure. CSIRO have developed a 'traffic light' system for this also.
Eye temperature may remain elevated beyond the 2 hour period in which animals display overt pain behaviour response (eg to acute event such as castration). The physiological process resulting from tissue injury is ongoing but the animals have acclimatised to the pain, so for pain therapeutics where incomplete pain control is anticipated beyond the peak duration of action of the therapeutic (such as castration) this could be problematic.

Blood sampling:

- Blood markers: cortisol is a commonly used and often unreliable measure. It is a marker of stress and not specific to pain. It may be elevated through the stress of the study rather than the painful operation.
- Acute phase proteins (haptaglobins etc) similarly unreliable especially in absence of infection.
- Metablomic and biomarkers: Not enough data yet to be of use for small ruminants and pain, with nothing in goats.

Dose rates

- The dose must be high enough to be as effective as possible, while safe across the classes of goats, as ideally it will be an S5 / used by producers, rather than veterinary prescription. When initial work in sheep they assumed that the cattle dose would work (0.5 mg/kg) and were surprised that a higher dose of 1 mg/kg was needed for efficacy. Subsequent work in meloxicam across other species supports this observation that meloxicam metabolism is highly variable between species. Goats are known to be rapid metabolisers, so we should assume that a higher dose than the sheep dose may be more efficacious. Colere's vox pol of vets in Australia and UK indicates that vets use a wide dose range between 0.25 and 2 mg/kg, indicating how little data there is for vets to access about meloxicam in goats.
- Studies have not seen any safety concerns with this dose rate and they generally feel that meloxicam is very safe in ruminants.
- In summary, we recommend that a dose response study should center around 2 mg/kg, if a pharmacokinetics data bridging study is undertaken first to provide insight in goat metabolism. The study could then include 1, 2 and 3 (or 4) mg/kg. There is not anticipated to be any measurable difference at 0.5 mg/kg increments.
  2mg/kg is strongly supported by trials to date as being safe and efficacious, however this must still be proved.

Pharmacokinetics

As previously discussed, given the known interspecies variability of meloxicam one of the first steps should be to generate a pharmacokinetic curve after administration of our product, in the target dose range, to obtain insight into its absorption, distribution and metabolism in goats. There are no published studies on meloxicam in goats at more than 0.5 mg/kg. one of our contacts have some non-published PK data on oral meloxicam tablets, 2 mg/kg (human grade; ground, bolus administration), as well as related data on residue depletion. They do not have the intention of publishing or registering.

Pharmacokinetic data will clarify how rapidly goats metabolise the product compared to sheep, and help confirm the target dose range for future dose response/ efficacy work.

We recommend in the first instance to undertake a PK data bridging study, using the team, laboratory and assay methodologies that they have used previously. This will provide the triple benefits of

providing critical PK data for the product in goats, and also enable us to bridge across to the data that they have already generated in goats, to give insight into anticipated dose efficacy, as well as residue depletion.

Residue Studies

There is currently no residue depletion work in goats at any dose above 0.5 mg/kg, and no published study at any dose to APVMA level. This work will need to be done, once the dose rate is determined.

APVMA generally requires GLP level for residues work. This is an issue in Australia as there are no labs accredited to GLP for such work, the closest is in NZ.

3. Conclusions

The team have increased confidence as to the path and likely success of achieving a registration (in some form) for meloxicam in goats. Engagement thus far with APVMA has been positive and helpful, when dealing with the permits team.

As with all registration processes of this nature (i.e. limited by available funds and focused on delivery of an outcome for industry) the next steps are characterised by selection of studies or work that answers the most critical questions balanced with learnings that help define the following steps. Ie. what is the most cost effective way to get to and through Stop/Go points.

3.1 Key findings

- APVMA has been made aware of the difficulties confronting the goat industry to obtain equitable access to pain relief as is available to other animal production industries.
- A single technical and detailed tier 2 PAA should be made to the APVMA, detailing all information known plus any scientific arguments, about meloxicam in ruminants and goats in particular. Each of APVMAs modules should be addressed. This application should ask targeted questions about data requirements. The APVMA will then provide a single technical response to the questions.
- Because there is so little data on oral meloxicam in goats, any study undertaken, where possible, should be published, and will greatly benefit the pool of knowledge to vets and producers in Australia and globally.
- Technical research undertaken across this project duration has:
    - Reviewed the published literature for meloxicam in goats, considering efficacy, safety and pharmacokinetics.
    - Connected with small ruminant pain researchers in Australia and USA.
    - Connected with goat vets in Australia and UK.
    - Considered the scope of Australian CROs having capability to undertake future work for GICA.
- Initial recommendations are:
    - Focus on an efficacy dose range of between 1 and 2 mg/kg

- Undertake a pharmacokinetics and data bridging study to enable refinement of the target dose.
- Start assembling the technical PAA dossier to submit to APVMA: requires a consolidated review of all literature, recent unpublished data, and scientific arguments across each area. Submit after the PK and bridging study has concluded with data.
- Once APMVA advice has been received, final advice can be provided on the type of efficacy study/ies, safety, and residues studies, and where the studies should be conducted.

3.2 Benefits to industry

While access to pain relief products is a high priority for the industry, there is a clear understand that the path and process to gain this access is complex and costs ill-defined. The project was designed to seek clarity in process and cost, before further commitment is made by industry. It is likely that this project will be one of the largest ever undertaken by this industry, and all effort needs to be made to maximise leverage and reduce unnecessary expenditure.

However it should also be noted that there is such a scarcity of published information that any work undertaken by the industry will be of high value to vets and producers regardless of the APVMA outcome.

Pain relief in sheep and cattle has been demonstrated to provide strong productivity gains through reduced weight loss (or increased weight gain) following husbandry practices, labour saving through easier stock handling and improved animal health outcomes. These types of improvements are expected to be equally reflected in goats.

4. Future research and recommendations

- **Undertake a pharmacokinetics and data bridging study**, and to enable bridging to the existing and in-progress work. Publish this study to maximise utility to vets.
- **Undertake a PAA (a tier 2 PAA; combination review +meeting)**
    - The aim of this is obtain written advice from the APVMA to the modules and levels required, and if possible, approval of the types of studies that may be acceptable. Sometimes the APVMA will also comment on measurables and statistical methods however this depends on the evaluator and program.
    - For a minor use permit label claim the preferred approach is to undertake a PAA with a meeting to present the issue to the Permits team and the Veterinary Registration team. A permit approach will be led by the Permits team, but the technical assessment will probably be led through the Vet Reg team.
- **Colere to complete a technical review on existing data for meloxicam in goats and other ruminants and prepare a detailed technical dossier (executive summary) and technical arguments, for an APVMA pre-application assistance tier 2.** This PAA submission must ask

targeted questions around what specific data APVMA would require to be satisfied, in each component.