Trilateral Joint Review: A First for Veterinary Drugs

Introduction

This case study focuses on international regulatory cooperation between Canada, Australia and New Zealand with respect to a joint review and simultaneous approval of a veterinary drug. The case study outlines the circumstances and cooperative efforts, including the benefits and challenges, which led to the first ever trilateral joint review of a veterinary drug submission: that of Metacam (meloxicam injection) for sheep.

For the purposes of this case study, the regulatory joint review of a veterinary drug is defined as the evaluation of a veterinary drug dossier that is shared by two or more economies[1].f A joint review is the concurrent evaluation of a dossier through a globally coordinated system of evaluations, peer reviews and report sharing. The responsibility for the review of the science components of the dossier is divided between different regulators, and other participating regulatory authorities peer-review the work of the primary reviewers for each particular technical section. The final review reports are used by all participating economies as the basis for their regulatory decisions. While each economy makes its own regulatory decision, efforts are made to have a harmonized regulatory decision.

Improved animal health and welfare, as well as increased productivity and food safety, constitute essential components of public health. In this context and that of globalized drug and agri-food industries, international collaboration can be a key tool to facilitate access to quality veterinary drugs for food producers and animal owners.

International joint reviews and work sharing on the assessment of veterinary drug dossiers are expected to increase the efficiency and effectiveness of drug approvals (registration/marketing authorization), facilitate simultaneous approvals of the drug in multiple economies and facilitate the timely access of new veterinary drugs to producers in many economies. Significant advantages can also be gained by regulators as joint reviews also facilitate and promote sharing information and knowledge, tapping into expertise, and building a community of international reviewers with expertise in related fields. Efficient and effective joint reviews, however, require a mutual understanding of the regulatory processes and responsibilities of each party involved, joint data requirements, common procedures, including setting food safety standards, and common timelines.

This document focuses on the process – the importance of the multi-regulator joint review of veterinary drugs, its benefits, and how such collaborations could be fostered in future.

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Characteristics of the international regulatory cooperation effort

Intended objectives of the cooperation

The primary objective was to run a pilot for the joint review of a veterinary drug by different regulators. In other words, this project aimed to test whether different regulators and veterinary drug sponsors could collaborate for a joint review, whether the same data package could satisfy the need of all participating economies, whether the review work could be shared by different jurisdictions, and whether the review reports prepared by reviewers from one economy could be utilized (following a peer review) by other regulators to meet their respective regulatory requirements. The regulatory decision informed by a joint review was expected to provide the same level of guarantee on the safety (both human and animal safety), efficacy and quality for the product when compared with the decision made by individual economies separately. In addition, the joint approval was intended to facilitate access to effective drugs in different economies at the same time.

The drug identified for the joint review was Metacam (active ingredient meloxicam), a non-steroidal anti-inflammatory drug for a novel use in sheep.

It was understood from the beginning that this joint review would focus on safety and efficacy assessments that are common in all three jurisdictions, but would allow each economy to address any economy specific regulatory requirements separately. In this joint review, safety and efficacy were jointly assessed. The economy specific requirement, only one in this case – the trade consultation for Australia – was handled by that economy alone, although other partners were made aware of this process.

Actors involved: trilateral cooperation, strongly aligned with international practices

The cooperation process was led by the relevant regulatory agencies and departments in Canada, Australia and New Zealand: Health Canada's Veterinary Drugs Directorate (VDD), the Australian Pesticides and Veterinary Medicines Authority (APVMA) and the New Zealand Ministry for Primary Industries (NZMPI). The three parties worked collaboratively to identify a willing drug sponsor that would submit the same data package to all three jurisdictions at the same time. Tasks were allocated in the following way:

- The APVMA was responsible for project management and acted as a central point of contact for the drug sponsor,
- The VDD was responsible for the food safety review and,
- The NZMPI was responsible for the target animal safety and efficacy review.

In addition, while this cooperation is the first joint review of a veterinary drug between these economies, international joint reviews of pesticides under the auspices of the OECD have been ongoing for some time, with this being identified as a priority area for OECD Members since 2004[2]. The veterinary drug joint review described in this paper followed the key principles of the joint review process now well established for pesticides. In particular, the approach taken and the process followed loosely mirrored

the OECD's Guidance Document on the Planning and Implementation of Joint Reviews of Pesticides[3].

Developing regulatory cooperation

The review of Metacam (active ingredient meloxicam) for sheep by VDD, APVMA and NZMPI is the first ever trilateral joint review of a veterinary drug. Before this cooperation, Australia, Canada and New Zealand had been collaborating for years on several technical areas of veterinary drug regulations, based on bilateral confidentiality arrangements. This, as well as management teleconferences or in-person visits, formed the foundation of confidence and facilitated the possibility of working together on a joint review.

In addition, the economies' participation in international fora has built a strong foundation for conducting a joint review. For example, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is a trilateral organization (represented by regulatory and industry organizations from the European Union, Japan and the United States) with the objective of harmonizing technical requirements for registration of veterinary drugs. Australia, Canada and New Zealand are observer members of VICH, and actively participate in both the Steering Committee as well as Expert Working Groups that develop guidelines for harmonized technical (data) requirements. Being observers to VICH, Australia, Canada and New Zealand consider VICH guidelines in their product registration processes, and therefore were able to use the same data package for the registration of this drug through the joint review. The many exchanges over the years between the three regulators at the steering committee meetings and through the various expert working groups have created confidence in our respective regulatory systems.

In addition to VICH, Australia, Canada and New Zealand also actively participate in the activities of Codex Alimentarius Commission and its committees, particularly the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). Codex is a joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Food Standards Programme that sets international food standards (e.g., maximum residue limits (MRLs) for veterinary drug residues in foods). Codex standards are based on the recommendations made by its independent science advisory committee – the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which are reviewed and adopted by all member economies. Experience in various Codex forums provided Australia, Canada and New Zealand with greater confidence in working together for the joint review and facilitated joint work in the area of assessment and recommendations for MRLs for residues of meloxicam in different tissues of sheep.

Confidence was also built through regular exchanges of information and in-person visits. Examples of information sharing exercises intended to develop a sound

knowledge of each regulator's review system, level of expertise and domestic challenges included:

- Sharing specific drug product related review reports;
- Ad hoc questions on technical matters and review files;
- Regular exchange of lists of recent approvals and workload related to drugs under review; and,
- A range of tele/video conferences and in-person visits in Ottawa, Canada. The APVMA attended meetings in Ottawa in 2004, 2008 and 2013, while the NZMPI visited Ottawa in 2004, 2010 and 2011.

Sheep production

Sheep production is a pillar of the agricultural sector in Australia and New Zealand. Canada relies heavily on these two economies for lamb imports. In 2014, Australia produced 720,600 metric tonnes of lamb, second only to China. New Zealand ranked third in the world (487,143 tonnes). In addition, Australia was the world's largest lamb exporter in 2013 (413,278 tonnes), followed by New Zealand (397,507 tonnes). Canada, which only ranks as the 75th largest producer of lamb, is a net importer. Lamb imports are an important component of Canada's overall agricultural imports, as it is the world's 15th largest lamb importer. In 2012, Australia and New Zealand supplied 96% of imported lamb to Canada. However, the lamb industry in Canada has room for growth and is the fastest growing meat protein on a per capita basis. Because sheep is a minor species in Canada, there may not be sufficient financial incentive for the pharmaceutical industry to register veterinary drugs in Canada for use in sheep at the same time as for use in major species. Consequently, although essential for efficient sheep production, there are not many veterinary drugs that are registered for use in sheep in Canada.

Given the importance of trade in lamb among Australia, New Zealand and Canada, the ability to access approved veterinary drugs allows producers to more effectively manage sheep flocks and increase production for greater consumer choice. The availability of medication to mitigate the pain associated with routine husbandry practices is vital in order to ensure ethical sheep and lamb production systems. While non-steroidal anti-inflammatory drugs for livestock have long been available to farmers, no such drug was specifically labelled for use in sheep in Canada until the approval of this drug in 2016.

Organization of the cooperation

All three regulators organized video/teleconferences on a quarterly basis, first to agree on proceeding with the joint review of this specific drug submission, then to assess the compatibilities of the review frameworks and assign technical sections to each economy. Over time, these video/teleconferences served to provide updates on the

status of each section's review and next steps, including timelines, data requirements, trade consultation dates. Scientific discussions between the regulators occurred throughout the review process.

Assessment: factors facilitating the cooperation

Common objective

In order to proceed with a joint review, interest from a drug manufacturer and from regulators was required. Because of the importance of sheep production in Australia and New Zealand, there was interest in a regulatory submission for Metacam for use in sheep. Because of Canada's growing lamb industry and lack of drugs approved for use in sheep, Canada shared this interest.

Effective regulatory systems

A joint review requires that all parties have effective existing regulatory requirements, as well as confidence in each other's regulatory systems. All three economies have effective regulatory systems that follow good regulatory practices. In addition, as detailed under the "developing regulatory cooperation" section above, the participation of all three regulators in international fora, such as VICH and Codex, regular exchanges of information and in-person visits were key to confidence building.

Confidentiality arrangements

The confidentiality of information and data submitted as part of the application, and assessments undertaken by the respective agencies, was managed under the applicable legislative framework for the regulation of veterinary medicines in each economy. Understanding their regulatory frameworks for veterinary drugs were comparable, all three regulators ended up signing confidentiality arrangements:

- 2005 Memorandum of Understanding between the VDD and the APVMA,
- 2005 Memorandum of Understanding between the APVMA and NZMPI, and,
- 2009 Arrangement between the Health Products and Food Branch (Health Canada) and the NZMPI.

As detailed above, such arrangements facilitated the exchange of review information, as well as ad hoc scientific and technical discussions, regular management teleconferences and in-person visits, all leading to a deeper trust amongst all three regulators, which was the base for this joint review to occur.

Outcome

In 2016, the drug was approved by all regulators for the alleviation of pain and inflammation in sheep. The review period lasted from April 2015 to April 2016, which

can be deemed a normal domestic review time in all three economies. This involved peer reviews of drafts and the complete review of files. The approval dates for Australia and Canada were April 28, 2016, while New Zealand approved the drug on October 26, 2016 (MRL promulgation date).

This joint review enabled simultaneous access to a new veterinary medicine in three major markets leading to improved animal health and food safety outcomes. In particular, given the smaller size of the sheep industry in Canada, the drug may not have been submitted for Health Canada review in 2015 if not for this trilateral joint review. Similarly, New Zealand is a small market for many veterinary pharmaceutical companies, which can negatively impact industry in that they may not have ready access to certain treatments where needed. The availability of joint review as a regulatory option helped facilitate greater product availability to New Zealand industry.

Benefits to regulators

Regulators benefitted from the potential to harmonise end points such as residue definitions, MRLs, and acceptable daily intakes (ADIs), which helps reduce barriers and disagreements to international trade of the animal commodity, thereby supporting trade between participating economies.

With respect to procedural aspects, regulators benefitted from:

- The shared workload and a reduction in the duplication of efforts for this joint review, which may have led to reduced resources being required to review the submission. In particular, Australia noted reduced regulatory effort as the primary reviews from Canada and New Zealand were utilized for decision making.
- Added robustness (and international consistency) to the decision making process through the sharing of scientific opinions of regulatory experts.
- A comparison of technical standards for assessments and risk appetites between the different regulators.
- A better understanding of how the other regulators operate and their policies and procedures, which leads to a better understanding of the rationale behind decisions. This also leads to opportunities for better (or more efficient) ways to manage regulatory processes and systems.
- The opportunity for staff to engage and work with other regulators; build networks of contacts and partnerships; maintain trusted partnerships; and share expertise.

Benefits to drugs sponsors

The pharmaceutical drug industry has identified the following benefits of the joint review to its members:

- Efficient use of company human and financial interests: generally, regulators have the same or similar questions for the product sponsor. The joint review meant the company addressed questions once, resulting in a reduced workload,
- It resulted in product registration in small markets like Canada. Otherwise, despite animal welfare issues and producer benefits, there would have been limited business interest in bringing the product to the Canadian market,
- Efficiency: one product – three shared reviews, three approvals at similar times.

Benefits for sheep producers

This outcome of this joint review provided Canadian sheep producers with simultaneous access to a medication with their Australian and New Zealand counterparts, which had never previously occurred. Sheep being a minor species in Canada, the market share for minor species drugs may not provide sufficient financial returns for drug manufacturers to invest in research and development, and a regulatory submission at the same time as in major markets. Consequently, few drugs are labelled for use in this species in Canada. Arguably, if it was not for this collaboration, a pain medication labelled for use in sheep may not have been available in Canada for years. The Canadian Sheep Federation expressed its support to this innovative review approach, to help them manage animal health and welfare, as well as to increase productivity and overall competitiveness.

Challenges

The challenges faced by the regulators in the joint review process ranged from structural (e.g. related to geography) to organizational. These include:

- Differences in regulatory requirements, data requirements and management of submissions including performance targets, i.e., timelines when a decision is to be made or how additional information requests are handled;
- The need for a sponsor with operations in participating economies willing to coordinate submission timing: ~ In this case, the existing regular exchange of submissions in queue between regulators facilitated this.
- Different time zones and geographical distance.
- Lack of a common submission platform (e.g., confidential information sharing site).
- Different methods of evaluation (e.g., the methodology to establish MRLs or withdrawal period) : ~ The ongoing work of Codex and JECFA has helped with such alignment and in the future, it would be of help for all regulators to use the JECFA method.

- Geographical differences in disease patterns (i.e., sensitivity and susceptibility of pathogens to treatments vary from region to region).

These challenges should be considered prior to future reviews. While structural challenges will remain, challenges of a more organizational or governance nature could be addressed in anticipation of further cooperation.

Regulators are mindful this was a pilot project and not a regularized practice which would need established procedures and require committed resources for allocation to joint reviews. For instance, one could see that common secure electronic platforms could increase the efficiency and speed of the regulatory information sharing. Similarly, the development of a standard procedure with timelines for such joint trilateral reviews would facilitate their being institutionalized.

Conclusion

Joint international reviews have been practiced for some years for the registration of pesticides. This first joint review of a veterinary drug submission was able to identify key success factors to consider for using this model in the future, including:

- A common objective to facilitate access to safe and effective veterinary drugs through efficient regulatory collaboration.
- Effective regulatory systems, following good regulatory practices, and mutual confidence in domestic systems.
- Economies collaborating in joint reviews should have comparable or harmonized technical/data requirements (e.g. as defined in VICH guidelines).
- Memoranda of understanding and confidential arrangements between the regulators.
- Transparent communication approaches and practices, and
- Good project planning and management, including an appreciation of the planning and time requirements for such collaboration, agreement by regulators and sponsors on timelines, and allotment of sufficient resources to meet timelines.

Confidence and trust building (between regulators, and between regulators and sponsors) is crucial to the success of the joint reviews – start small: with less complex submissions at the beginning; promote regular exchange of information and scientific interactions (both at senior management and scientific staff levels) even for other projects and activities.

Regulators must also recognize that their independent review decision making remains at the forefront. For instance, in the case of this review, final MRLs for Metacam were similar in Canada and New Zealand, but different in Australia.

Owing to the success of this pilot review, a second and more complex joint trilateral review between regulators from Canada, Australia and New Zealand was completed in late 2022. As planned, this review built on the previous work and laid the groundwork for an ongoing collaborative process.

Endnotes

[1] Adapted from the Joint Review of a pesticide, OECD Guidance Document on the Planning and Implementation of Joint Reviews of Pesticides, Series on Pesticides, No. 60. https://www.oecd.org/en/publications/guidance-document-on-the-planning-and-implementation-of-joint-reviews-of-pesticides_9dec72f5-en.html

[2]OECD (2008), *The Business Case for the Joint Evaluation of Dossiers (Data Submissions) using Work-sharing Arrangements*, Series on Pesticides No. 41, ENV/JM/MONO(2008)1. https://one.oecd.org/document/ENV/JM/MONO%282008%291/En/pdf

[3] OECD Guidance Document on Planning and Implementation of Joint Reviews of Pesticides, Series on Pesticides, No. 60: https://www.oecd.org/en/publications/guidance-document-on-the-planning-and-implementation-of-joint-reviews-of-pesticides_9dec72f5-en.html

Date: Finalised in 2022.