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Veterinary Biologicals and Animal Feeds
Department of Agriculture, Fisheries and Forestry

Submission via Haveyoursay website:
Review of the biosecurity risks associated with veterinary immunobiologicals - Agriculture hub

Dear Veterinary Biologicals and Animal Feeds team,

RE: Animal Biosecurity Advice 2024-A03 - Issues Paper – Review of the biosecurity risks associated with veterinary immunobiologicals

Thank you for inviting comments on the *Animal Biosecurity Advice 2024-A03 – Issues Paper – Review of the biosecurity risks associated with veterinary immunobiologicals* (the Issues Paper). We appreciate the opportunity to provide preliminary comments in advance of the policy review.

Animal Medicines Australia (AMA) is the peak industry body representing the leading animal health companies in Australia. Our members are innovators, manufacturers, registrants and suppliers of a broad range of veterinary medicines. Our members work at the cutting edge of animal health science to prevent, control and treat disease across the livestock, equine and companion animal sectors. Products from our member companies account for more than 90% of all animal health products in Australia.

Key principles

AMA considers it essential that:

- biosecurity policies for veterinary immunobiologicals prioritise risk-based assessment and are underpinned by science;
- import control measures, regulation, compliance and enforcement activities are proportionate to the risk/s posed;
- administrative burden and regulatory duplication is minimised wherever possible;

- biosecurity import policies and processes consider both current and future threats, and have sufficient agility to respond appropriately and efficiently to sudden shocks (such as disease incursions or disruptions to supply chains); and
- transparency, accountability and communication with applicants on requirements, timeframes, decision-making processes and the rationale for decisions is prioritised.

The role of animal medicines in biosecurity

AMA member companies play a vital role in Australia's biosecurity as the producers of medicines that prevent, control and treat animal diseases across the livestock, equine and companion animal sectors.

AMA members develop, register and supply innovative new medicines including vaccines and anti-infection medicines to prevent and control outbreaks of animal disease, enable good health and wellbeing, and support the production of food and fibre products that are safe for human consumption and use. Healthy animals are much less susceptible to disease and infection, and good animal health is essential to good animal welfare. Australia is in a unique position because many of the world's most devastating and debilitating animal diseases are not present here. Our strict biosecurity measures and systems help maintain this disease-free status, protecting animal health and welfare, public health, environmental health, food quality and safety, and give Australia a competitive advantage in global markets.

Animal disease incursions pose serious risks to animal health and welfare, productivity and sustainability. The World Organisation for Animal Health (WOAH) estimates that more than 20% of animal production worldwide is lost as a direct result of animal disease.[1] Without access to animal health products such as vaccines, antimicrobials and parasiticides, farm productivity would be reduced due to:

- higher farm input costs per unit of production, which are often passed on to consumers,
- sick animals being less productive, thus reducing returns on farm investment,
- higher animal mortality due to illness or disease, leading to falling stock numbers and the loss of valuable genetic lines, and
- more labour-intensive stock management practices to control and manage disease on farm.

Australia's biosecurity at international, national, regional and local levels, and industry-led disease preparedness and response processes, including access to disease prevention tools such as vaccines, are central to maintaining animal health and keeping animal diseases out of Australia.

AMA recognises that climate change, shifting and unpredictable trade and travel patterns, and changes in land use pose multiple, emerging and complex risks to Australia's animals, people, environment, economy, livelihoods and way of life. Australia's biosecurity policy settings will need to have sufficient flexibility to respond efficiently and effectively to emerging risks across time and space to protect Australia's people, animals and environments.

The impact of regulatory settings on biosecurity

Regulatory settings are an important component of biosecurity. The ability of animal health companies to maintain business continuity and the capacity to develop and provide critically important veterinary

[1] ANIMAL-HEALTH-EN-FINAL.pdf (woah.org)

medicines depends on a regulatory environment that is reliable, efficient and predictable. Disruptions in supply chains related to the COVID-19 pandemic illustrated the need for flexibility and adaptability in the biosecurity system to mitigate the impacts of external stressors when 'business as usual' is not possible.

It is important that biosecurity policies have the capability and flexibility to respond quickly to emerging threats and emergency situations. For example, in the event of exotic disease detection, it is critical that veterinary medicines can be brought into Australia quickly and efficiently to address an animal disease threat, including medicines that may not be routinely held in Australia and those that are not currently registered for use here.

Policies and regulatory settings should be based on science and risk-assessment, with systemic agility to fast-track emergency approvals and permits, clear imported medicines quickly through Australian borders, supply effective distribution networks (especially to rural and remote areas) and with risk-based flexibility in satisfying non-critical regulatory requirements.

Question: What has been your experience in working with the department on importing veterinary immunobiologicals into Australia?

As manufacturers and suppliers of imported veterinary vaccines to the Australian market, AMA members have extensive experience working with DAFF for both import permits for veterinary vaccines, ingredients for manufacturing and risk assessments for proposed new products. In general, the department has been working well with industry to ensure appropriate access to veterinary immunobiologicals for the Australian market without compromising Australia's biosecurity. Communications from the department are generally thorough and helpful in defining requirements and assessing cases for equivalence.

In particular, the Animal & Biological Imports Branch (ABIB) has worked well to ensure applications are assessed in a timely manner to ensure a continued supply of immunobiological products into Australia. It is also acknowledged that Animal Biosecurity Branch (ABB) have worked well in accepting high quality scientific arguments to demonstrate equivalence to current policy positions.

Timelines for approval of import permits can sometimes be longer than expected which can negatively affect supply chains. This has been particularly evident in recent months. It would be helpful to extend Permit approvals (eg: from 3 years up to 5 years), with the onus on the manufacturer to update details if/when the biosecurity risk changes.

Applications where consideration of equivalence is required represent a considerable bottleneck to approval timelines:

- For industry, there is a lack of understanding on the division of responsibilities between the ABIB and the ABB. Which applications require deferral to the ABB, and which decisions can be made by the ABIB alone?
- For applications referred to the ABB, there is no visibility on the timelines, decision making process and the rationale for the final outcome. Past decisions by the ABB are not broadly communicated to industry, which results in resources being committed to generate arguments for cases where the ABB have already made a positive determination.

Greater transparency into these processes would assist industry in their planning to ensure timely access to new immunobiologicals and continued supply of existing immunobiologicals.

Duplication or triplication of submissions/assessments can exist where APVMA and/or OGTR consideration is required. Alignment and collaboration on regulatory and administrative requirements between regulators would provide important efficiencies for both regulators and industry.

Question: Australia's biosecurity policies impact the availability of veterinary immunobiological products in Australia. Are there products marketed offshore that would be useful to you that are not currently available in Australia?

AMA member companies regularly receive enquiries from veterinarians and other stakeholders in Australia who would like to gain access to vaccines that are registered and marketed overseas but not in Australia. Similarly, there are vaccines that could be useful in managing animal diseases in Australia for which Australia's biosecurity policies influence the commercial decision to pursue registration in Australia.

Extraneous agent testing

The extent of extraneous agent testing is a significant barrier to importing innovations to Australia, as it appears to be excessive, particularly for companion animals, and for inactivated companion vaccines.

BSE/TSE policy

Most immunobiologicals are manufactured using a seed lot system where a defined master seed is used to create downstream material for routine production of immunobiologicals. Many of the veterinary medicine regulators globally use the master seed as the starting point for their regulatory assessment. Therefore, regulatory documentation and recordkeeping for the master seed is generally very robust.

In contrast, DAFF requires both a defined chain of custody and evidentiary documentation supporting the manufacture of the immunobiological product from the *original isolation* of the vaccine material. In general, such information is impossible to obtain, as the original isolation could be related to clinical or research efforts performed at a university and not originally intended for vaccine development. Such work is generally performed decades before development on the vaccine candidate commences. Therefore, robust documentation on exact batches of raw materials used, or exact culture or isolation methods, is usually not available.

The robust documentation requirements of contemporary immunobiological manufacturers assure the BSE/TSE-free status of all raw materials used from the master seed to the finished product. Furthermore, many of these vaccines have been supplied to overseas markets for years without any detection of prion disease associated with these products, including countries that are established as BSE/TSE negligible risk, similar to Australia.

Finally, unlike extraneous agents testing, retrospective testing of BSE/TSE status of seed material is not possible. Therefore, without extensive existing documentation of pre-master seed stages, and with the current policy position, such vaccines will remain inaccessible to Australia.

Geographical location of Pathogens of Highest Concern

The manufacturing sites of many global leaders in veterinary vaccines handle Pathogens of Highest Concern. This could be to support efforts in R&D or for the purpose of commercial vaccine manufacture. The current policy and interpretation relating to the acceptability of these sites for the purposes of importing to Australia is problematic. Companies run the risk of being left out of significant R&D programs and commercial developments.

All vaccine manufacture occurs under Good Manufacturing Practice (GMP) standards or equivalent. The potential for cross-contamination is managed effectively. However, AMA recognises that there may be concerns for some manufacturers.

AMA suggests that an alternative approach could be a minimum set of criteria that a manufacturer has to meet to support supply from such a site (most likely derived from cases for equivalence), plus a site audit to confirm these criteria are being met, rather than the current policy which indicates that these vaccines cannot be imported into Australia.

Lack of international harmonisation

It is acknowledged that the live and inactivated vaccine policies and the summary of information documents require updating. References to international regulatory guidelines within those documents are outdated and should be revised to align with contemporary Ph. Eur. and US CFR references.

Furthermore, greater harmonisation between existing DAFF policy and global regulations would be beneficial. For example:

- Ph. Eur. have moved to a risk based approach for consideration of additional extraneous agents testing (*Ph. Eur. 2.6.37. Principles for the detection of extraneous viruses in immunological veterinary medicinal products using culture methods*). Such an approach has not yet been generally adopted by DAFF. This creates a greater burden on manufacturing sites to maintain specific testing for the Australian market where such testing has been waived for other markets.
- DAFF maintains its own list of BSE-affected countries (*Bovine Spongiform Encephalopathy (BSE) Country list*) instead of aligning with the WOAH Official Disease Status.
- Test methods described in *Review of published tests to detect pathogens in veterinary vaccines intended for importation into Australia (2nd edition)* have not been updated in over a decade. Specific testing described in the review is also not aligned with generally acceptable, validated, testing methodologies that have been approved by other international regulators.

Greater harmonisation between DAFF's policies and regulations with their international counterparts would make the Australian market a more attractive prospect for overseas manufacturers.

Question: How can the department's biosecurity policies better support Australia's immunobiological production sector?

Clear guidance materials are essential to ensure applications are correct and complete when first submitted, and to reduce the time lost resolving non-technical issues. Improved guidance material would be welcomed for technologies that are relatively new to Australia, such as monoclonal antibodies, to support shared interpretation and mutual understanding by both the regulator and the applicant.

Responses to other questions in this document also indicate ways in which the department could better support the immunobiological sector.

Question: As a domestic producer of veterinary immunobiologicals, what challenges do you face when importing biological goods that are produced offshore?

Numerous challenges are encountered when evaluating new or existing products for importation into Australia:

Regulatory harmonisation

There is no alignment between international and Australian biosecurity policies and regulations. Therefore, additional resources are required to maintain Australian-specific requirements which may not be viable for a relatively small market compared to EU and USA. This is a significant barrier to the introduction of innovative immunobiological products into Australia.

Renewal process

The current import permit renewal forms require applicants to confirm that no changes to manufacturing, sourcing of ingredients and testing have occurred. However, in recent years there has been an observed trend in the renewal process of both pharmaceutical and immunobiological import permits for more evidentiary documentation to be supplied.

Current anecdotal experience is that renewal documentation requirements mirror that of a full new product application. This includes full evidentiary documentation of sourcing of raw materials, testing of raw materials and finished products, evidence of site procedures and more.

Such additional documentation requirements are not currently disclosed on the renewal form and are only raised during the evaluation process. This causes considerable pressure on overseas sites to produce documentation that was not initially expected. A supply risk is also likely when such requests for further documentation are raised late in the evaluation process, or even during the delegate review phase.

Other documentation concerns

The evidentiary documentation that is required for low risk commodities (e.g. purified and highly processed), or commodities that are already "effectively sterilised", is excessive. This could include requests for detailed sourcing, processing or testing information of precursor materials or raw

ingredients used to manufacture the immunobiological. Such information is often not held by, or is highly confidential to, our suppliers. In some cases, information from sub-suppliers is required. Such excessive documentation requests may jeopardise the relationship between manufacturers and their suppliers, especially when no other authority is requesting similar information. Documentation requirements should clearly reflect the risk that is being managed and be scientifically justified.

Seed lot terminology

The current definition of "production" does not align with terminology used by most manufacturing sites. In general, manufacturing sites consider production to be processes associated with routine production, generally from the "production seed" to finished product. The master seed and working seed are not considered production.

However, the DAFF policy considers the working seed as part of production. This causes issues with overseas manufacturing sites, where details of obsolete, historical raw materials are captured on the import permit. Manufacturing sites are obliged to review historical records with every renewal for working seeds that have not changed in many years.

SPF Eggs Contingency Amendment

Specific pathogen free (SPF) eggs are a critical component used in the production of both human and veterinary vaccines, quarantine monitoring, sentinel programs, diagnostics and biomedical research. There are very few producers of SPF eggs in Australia and a growing demand for vaccines. Flock breakdown poses significant risks to the continuity of supply of Australian-produced SPF eggs and importation of SPF eggs from overseas may be necessary to address critical needs. There have been multiple recent examples of shortfalls in local SPF egg supplies, leading to vaccine supply disruptions and posing risks to many critical animal disease control programs.

The SPF Egg Contingency Amendment 2006 (enacted in 2022) is a positive example of regulation that supports local manufacture of vaccines. Importation of SPF eggs from overseas is facilitated when local supplies are impacted for various reasons, providing appropriate risk management and supporting local manufacture and supply chains. There may be potential to develop contingency plans for other products of animal origin, balancing risks and ensuring supply continuity of critical vaccines.

Question: What new manufacturing technologies for veterinary immunobiologicals need to be recognised in Australia's biosecurity policies?

The list of technologies proposed in the Issues Paper is not exhaustive. Researchers may have examples of additional novel manufacturing technologies and/or immunobiological products that should be accommodated. AMA notes that some new technologies may be commercially sensitive or under intellectual property protections and thus may not be identified publicly. AMA would suggest that sufficient flexibility is built into biosecurity policies and processes so that new innovations can be brought to Australia.

AMA offers the following two examples where the current policies would benefit from amendments to facilitate the use of two common manufacturing technologies:

(a) Molecular cloning

The use of molecular cloning techniques in generating vaccine candidates is becoming more widespread with a greater focus on nucleic acid-based vaccine technologies. Whilst such techniques are already utilised to generate recombinant subunit vaccines that are already in the Australian market, the biosecurity aspects of molecular cloning are not specifically addressed in the current policy.

The use of synthetic nucleotide templates, non-animal origin reagents and buffers, highly purified enzymes and several rounds of chemical, physical or chromatographic purification results in an extremely low biosecurity risk vaccine antigen.

(b) Effective sterilisation

The definitions of effective sterilisation should be expanded to include any validated ionising radiation treatment and also refer to continuous flow sterilisation technologies.

Question: As a manufacturer of immunobiologicals, what production standards are relevant to the biosecurity risks posed by the importation of veterinary immunobiologicals?

Harmonisation with guidelines from other regulatory authorities is supported (particularly the EU pharmaceopoeial standards and Title 9 of the Code of Federal Regulations (US)). Manufacturing facilities for vaccines operate under the principles of Good Manufacturing Practice. Alongside the high standards prescribed by the European Pharmacopoeia (Ph.Eur.) and the Veterinary Services Memoranda (USDA), immunobiological products that are manufactured under GMP and with traceability of materials of animal origin, are supplied to major markets (including the EU and USA) and pose low biosecurity risk.

Question: Are there any pathogen species associated with imports of veterinary immunobiologicals that have not been listed by the department (see Attachment A – Hazard Identification)?

The current list in Attachment A is comprehensive. We would like to highlight that the list in Attachment A includes organisms that are currently not in the existing Annex 1, 2, or 3 lists. AMA suggests that these lists are regularly reviewed for both new pathogens of concern, but also where new surveillance data has indicated a pathogen has become endemic in the population.

Question: What changes have you seen in demand for immunobiological products in Australia or overseas? What are the drivers for this change in demand?

Local disease outbreaks are key drivers for demand. A current example is the demand for vaccines against Leptospirosis in dogs with several outbreaks of disease emerging in recent years. Leptospirosis vaccination is often not part of the standard vaccination protocol for many pets, and increased demand for vaccination with these outbreaks exceeded usual supply volumes. Production issues in the global

manufacturing sites resulted in significant supply disruptions and periods of unavailability, with veterinarians unable to provide booster doses or initial vaccinations for new dogs.

AMA members operate in a global industry and monitor international trends in demand for immunobiological products through their overseas divisions. Veterinarians are also well aware of products that are available in other markets and look to guidelines and key opinion leaders (e.g. World Small Animal Veterinary Association) to improve their practice.

If we can provide any further information or clarification on any of the points raised in this submission, please do not hesitate to contact me.

We hope that this information is of assistance to the review team and look forward to further engagement as the policy review process progresses.

Yours sincerely,

Dr Charmian Bennett
Director Science and Policy