Independent review of the agvet chemical regulatory framework

Submission from the

Australian Veterinary Association Ltd.

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Contents

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Introduction

The Australian Veterinary Association (AVA) is the national organisation representing veterinarians in Australia. Our 9,000 members come from all fields within the veterinary profession. Clinical practitioners work with companion animals, horses, livestock and wildlife. Government veterinarians work with our animal health, public health and biosecurity systems while other members work in industry for pharmaceutical and other commercial enterprises. We have members who work in research and teaching in a range of scientific disciplines. Veterinary students are also members of the AVA.

Executive summary

Veterinary Medicines: Key points

1. Access to veterinary medicines for all (>1,000) species
2. Quality of products essential
3. Efficacy (and effectiveness) important for registered products
4. Effectiveness necessary for all products
5. Safety necessary for all products
6. It is an unreasonable expectation that registration will be possible for all products, actives or formulations which are likely to be required for the treatment and management of animal health and welfare.
7. Registration of all veterinary medicines for production animal species desirable, especially with respect to MRLs and WHPs. However, there will be circumstances where a registered product is not appropriate OR it is required to be used at a different dose rate, frequency or duration and support is required to enable veterinarians to establish an appropriate WHP
8. Registration of major products for other animal species desirable
9. The disease spectrum presented to veterinarians, especially those in non-production animal species is extensive, with many parallels to the requirements placed on their medical colleagues
10. For unregistered products systems for collecting real world data (RWD) and real world evidence (RWE) to support dose regimens, effectiveness, and safety desirable
11. Undergraduate training and continuing professional development of veterinarians provides a solid foundation for the appropriate and responsible use of veterinary medicines, whether the products are registered for animal use or not registered.
12. Veterinarians have responsibilities for animal health and welfare. A major component of veterinary responsibility in herd/flock health is to manage risks from the use of a range of veterinary medicines, both prescription and non-prescription. This includes when it may not be appropriate to administer a specific registered product (for example, due to physiological or environmental factors which are likely to impact efficacy/safety/residues if used

according to the registered label). A real-life example has been sheep with significant subacute liver damage due to phomopsin.

13. Within the One Health area, veterinarians work closely with other professionals to protect animal, human and environmental health.
14. Veterinarians are at the forefront of infectious disease emergence from wildlife and need to respond quickly and effectively, often requiring access to specific veterinary medicines, especially vaccines.
15. A regulatory system that facilitates and supports the availability of veterinary medicines and works closely with the veterinary profession is the most desirable outcome.
16. A regulatory system that aims to be world leading must support timely availability of innovation. Close collaboration with veterinarians through the control of use legislation will facilitate effective use.
17. The most refined and responsive system of veterinary medicine availability and individualisation requires ongoing monitoring of use with appropriate and timely feedback to allow targeted modifications.
18. A regulatory system would benefit from a visible connection between the regulatory system and the social license of producer industries. Veterinarians are increasingly involved at the coalface of many producer industries, have responsibilities for animal health and welfare and as such could play an influential role in connecting the regulatory system to current and future use of veterinary medicines.
19. Diagnostic tests can often underpin accurate diagnosis and the development of treatment plans. Such test should be accurate and reliable and validated to ensure they provide appropriate information. There is currently no requirement to validate diagnostic tests.

Availability and use of veterinary medicines in the decades ahead

The comments developed by the AVA in response to the Issues Paper of the AgVet Chemical Review were prepared in the context of an evolving veterinary profession.

Animals under the care of the veterinary profession

While there is a strong trend towards veterinary practice consolidation to capture the commercial and professional benefits of large scale, the veterinary profession itself is becoming increasingly focused on the needs of its clientele. For both production (food and fibre production) animal and companion animal practice there is a growing expectation for precision of diagnosis and treatment with an emphasis on preventive interventions. Similarly, there are expectations for a similar sophisticated and continuously refined approach to the health and welfare of wildlife, exotic animals, and zoo animals. While cattle (dairy and beef), sheep (wool and meat), pigs (meat) and poultry (meat and eggs) dominate food animal practice, there are many other less numerous production animal species including goats, alpacas, camels (milk and meat), game birds, bees and aquaculture species. Each species, irrespective of its numbers, has its own requirements for veterinary professional intervention and unique needs for veterinary medicines. Indeed, for some livestock industries, the activities of many practitioners (eg pig, poultry, sheep, feedlot) are directed almost exclusively towards flock/herd health and/or the management of veterinary medicine use, rather than traditional single animal clinical medicine. Veterinarians engaged in such practice have developed considerable expertise relevant to the management of risks associated with agvet chemical use.

According to a recent survey (Animal Medicines Australia and Newgate Research, 2019) veterinarians in small animal practice are available to attend to the needs of an estimated 5.1 million dogs, 3.8 million cats, 11.3 million fish, 5.6 million birds, 614,000 small mammals, 364,000 reptiles and 1.8 million 'other' pets. The relationship between owner and pet is extraordinarily important. The same survey reported that over 60% of dog and cat owners refer to their pet as a member of the family and most spend an average of 3-4 hours with their pets every day. Around half of all dog and cat owners allow their pets to share their beds, and more than 25% take their pets on holidays or road trips. Clearly there exists an extraordinary need for veterinarians to have access to high quality veterinary medicines to support the health and welfare needs of companion animals.

Access to high quality veterinary medicines

There is an important distinction between production animal medicine and the medicine of all other species.

Production animals, producing food (meat, milk, eggs, honey) and fibre (wool, cashmere, mohair, alpaca fleece and other fibres), are raised to meet specific food safety, health, welfare, trade and other standards. As a consequence of these production standards the nature of the medicines available to support the health and welfare of individual animals and groups of animals is very limited and not expected to change in the future. A significant consideration is that of tissue residues following treatment and the need to ensure that maximum residue limits (MRL) are not exceeded, often requiring the need for a withholding period (WHP). When an MRL is not available or when products are used in a way other than described on the label (extra-label use or ELU), veterinarians must consider the impact of tissue residues in edible produce on human health and trade and formulate recommendations, usually by use of a WHP, to ensure that produce is safe and meets the often stringent standards applied domestically and by trading partners.

For companion animal and other non-production animal species veterinarians are currently permitted to use veterinary medicines registered by the APVMA or veterinary medicines acquired from other sources, for example products registered by the TGA for use in humans. The need for an increasing formulary of veterinary medicines is driven by an increasing number of species presenting for veterinary attention and the significant role played by animals in the lives of their owners. There is an expanding number of health and welfare problems requiring treatment, often for extended periods, even the lifetime of the animal being treated. Infectious and non-infectious diseases are treated. Endocrine disorders such as hyperadrenocorticism, diabetes and hyperthyroidism; a diverse array of cancers; heart disease, skin disease; epilepsy and other CNS disorders; reproductive disorders; urinary tract disorders, musculoskeletal problems, notably osteoarthritis; ophthalmological and ontological disorders – all increasingly demand attention and a high standard of management. Infectious and parasitic diseases due t to a diverse range of biological agents which may not necessarily manifest consistently or as classical disease increasingly require veterinary investigation and treatment. The possibility of the emergence or of new manifestations of disease due to prokaryotic and eukaryotic pathogens, perhaps associated with environmental or husbandry changes, cannot be reasonably anticipated by a registration system and the veterinary profession provides an essential reserve to ensure that both productivity and animal welfare are adequately protected in such circumstances.

Ideally, all veterinary medicines are subject to the rigorous quality, safety and efficacy requirements of the APVMA. However, this is not the case and has not been the case in recent decades and perhaps is less likely to be the case in the future.

A survey was undertaken in 2010 to identify the veterinary medicines (Prescription Animal Remedies or Schedule 4 medicines) recommended during undergraduate training of veterinarians in Australia and New Zealand together with the veterinary medicines recommended in a number of authoritative veterinary pharmacology textbooks and formularies (Mills et al 2010). A total of 978 recommended active constituents was identified. At the time there were 223 active constituents in veterinary medicines approved by the APVMA. Only 23% of the recommended actives were available in registered products. This has not changed significantly in the 10 years since this survey was undertaken.

A total of 20 pharmaceutical active constituents were lost from the APVMA in last decade (2010-2020): amphotericin B; aspirin; cinchocaine; corticotropin (ACTH); difloxacin; etamiphylline; etiproston; etodolac; gramicidin; histamine; ketanserin; meclofenamic acid; medroxyprogesterone acetate; nonoxynol-9; penicillin G (benzylpenicillin); phenytoin; porcine somatotropin (PST); quinalbarbitone; ramifenazone; and tripelennamine. While a total of 19 pharmaceutical active constituents were gained in last decade (2010-2020): pergolide (approved 2010); robenacoxib [ONSIOR TABLETS / INJECTION FOR DOGS / CATS] (2010); thiamazole [FELIMAZOLE COATED TABLET (treatment of feline hyperthyroidism)] (2012); dexmedetomidine [DEXDOMITOR INJECTABLE SEDATIVE AND ANALGESIC FOR DOGS / CATS] (2012); carbimazole [VIDALTA TABLETS FOR CATS (treatment of feline hyperthyroidism)] (2013); dirlotapide [SLENTROL (obesity in dogs)] (2013); imepitoin [PEXION TABLETS FOR DOGS (antiepileptic)] (2015); oclacitinib [APOQUEL TABLETS FOR DOGS (antipruritic)] (2015); pradofloxacin [VERAFLOX TABLETS FOR DOGS / CATS ANTIMICROBIAL] (2015); telmisartan [SEMINTRA ORAL SOLUTION FOR CATS (reduce proteinuria in cats with chronic kidney disease)] (2015); clodronic acid [OSPHOS SOLUTION FOR INJECTION FOR HORSES (reduce lameness)] (2016); peforelin [MAPRELIN (synchronisation of oestrus in sows)] (2016); terbinafine [OSURNIA EAR GEL FOR DOGS (antifungal)] (2016); triptorelin [OVUGEL (TRIPTORELIN ACETATE) GEL FOR INTRAVAGINAL USE IN SOWS (synchronisation of oestrus in sows)] (2016); amlodipine [Amodip

Flavoured Tablets for Cats (treatment of hypertension)] (2018); lokivetmab [CYTOPOINT Solution for Injection for Dogs (atopic dermatitis)] (2018); cimicoxib [CIMALGEX CHEWABLE TABLETS FOR DOGS (NSAID)] (2019); plasmid DNA (rE. coli DH5α pINGhT) [ONCEPT® CANINE MELANOMA VACCINE] (2019); and budesonide [DERMCARE BARAZONE BUDESONIDE LEAVE-ON CONDITIONER] (2020).

However, it is not only active constituents that are needed. The actives need to be formulated into a dosage form that is suitable for the animal to be treated. For example, formulations are needed that can be given by a suitably safe route of administration to an angry chihuahua or a feral cat where there are few potential reliable routes of administration. In view of the vast number of animal species, spanning mammals (placental (monogastric and ruminant), marsupial, monotremes), birds, reptiles, amphibians, fish, and invertebrates such as insects and arachnids, there can be a huge number of formulation types needed. In addition to species variation, variation of size within and between species is immense. For a small animal practitioner, the smallest patients may be in the grams (mouse, say 30-80g), to the largest great Dane (could be around 94kg). Even within dogs, the smallest would be around 800g. There is an increased client demand about preference for animal treatment, if the companion animal does not like taking medications this can negatively impact the human animal bond, causing stress and risk of injury for the owner

The regulatory process is expensive. Pharmaceutical companies are not philanthropic. Only unmet needs likely to generate a return on investment will gain the interest of the global and domestic pharmaceutical companies. While very common problems are often well catered for with veterinary medicines, many of the species requiring treatment are considered by regulators as minor (but not considered minor by their owners) and many of the indications for treatment are minor (from the perspective of number of animals at risk). The multitude of minor use, minor species – MUMS – needs is unlikely ever to be addressed by the current regulatory approach.

To enhance and facilitate the development and approval of new veterinary medicines the Center for Veterinary Medicine of the US Food and Drug Administration (FDA) has recently released five guidance documents. The guidelines present new approaches to demonstrate substantial evidence of effectiveness or a reasonable expectation of effectiveness and include the use of adaptive study designs (CVM 2020e), use of biomarkers (CVM 2002d), use of studies from foreign sources (CVM 2020b), the use of real-world data and real world evidence (CVM 2020c), as well as incentives and programs to support the approval of new veterinary medicines for MUMS (CVM 2020a).

However, it should not be overlooked that significant animal health diseases with high morbidity or mortality or zoonotic potential are also increasingly devoid of effective medicines. This is particularly evident in the areas of bacterial infection and parasitic infection. Resistance to available treatments (antimicrobial resistance and antiparasitic resistance) has rendered existing treatments inadequate. New treatments not affected by the current resistance mechanisms are not expected to become available principally because of the enormous cost of discovery and development and the uncertain regulatory environment. The emergence of resistance to all available treatments in liver fluke (*Fasciola hepatica*) of sheep and cattle and resistance in various nematode species in cattle, sheep and horses is becoming a dire problem with substantial impact on animal health and welfare.

Alternative sources of veterinary medicines

An important and widely used source of veterinary medicines is derived from extra-label (ELU) use (also known as (off label use) of registered veterinary medicines. ELU is defined as any use of a product that is not described in the label of the product and most commonly applies to use in the labelled species for a new indication or at a new dosage regimen (route of administration, dose rate,

frequency, duration) or use in an animal species not included on the label. ELU often required, for example, when there is a need to use a medicine in uncommon species such as alpacas and a potentially suitable medicine is registered for cattle and sheep. If regulatory overview is beneficial then minor use permits can be sought from the APVMA, but in practice are expensive, time consuming and complex to obtain, where the benefit is often much less than the effort.

A significant issue associated with ELU in food producing animals relates to the maximum residue limit (MRL) (whether one is available or not available) and the need to determine a withholding period (WHP) that allows residues associated with the ELU to deplete to concentrations less than the MRL. This is an issue that needs to be resolved by consultation and collaboration with the various regulatory agencies with an interest in tissue residues (for example, APVMA and FSANZ and importantly the NRS) by the veterinary profession and other key stakeholders (including the major meat and egg industries). Using real world evidence (described further later in this introduction) it is very possible to monitor the effectiveness of each WHP recommended for each ELU by having tissue samples analysed for residue content at the end of the WHP. The information from this monitoring would have enormous benefits in allowing a uniform and evidence-based approach to WHP determination and recommendation.

ELU in the multitude of species not used for food production does not require consideration of WHPs. However, capturing information on the effectiveness and safety of this ELU will also have significant benefits in refining the treatment of new species.

Compounded Veterinary Medicines

Compounded veterinary medicines (CVMs) have recently begun to fill the large gap between registered veterinary medicine and unmet need. In recognition of the important role of compounded medicines and the absence of regulatory clarity the AVA have prepared and distributed guidelines for the preparation and use of compounded pharmaceuticals (AVA 2020a). However, there is also a need to define Good Compounding Practice for Veterinary Medicines (GCPvm) and to ensure that it is implemented. This is a task that the AVA are currently working on via the AVA Veterinary Compounding Working Group.

How important are CVMs to veterinary practice?

A survey of AVA members was undertaken in June 2020 to inquire about the use of CVMs in contemporary veterinary practice. A total of 747 responses were received. Respondents were from 39% suburban, 22% urban and 31% rural practices, with the majority of the case load being companion animals in 71%, mixed practice in 14%, equine practice 9%, with zoo, exotic and unusual pets being the major focus in 2%.

In this study, 82% of responding veterinarians reported using CVMs, but frequency of use was low (71% of responding veterinarians used CVMs once or less each day).

With respect to adverse drug reactions, 81% of respondents reported no ADRs associated with CVMs, while 19% had experienced at least one ADR, 1% described frequent ADRs, 1% saw ADRs at the same frequency as with registered veterinary medicines and the remainder (17%) reported ADRs occasionally to extremely rarely.

While use of CVMs is much lower than the use of registered products, CVMs nevertheless occupy an important role, which is likely to expand in the decades ahead. The absence of specific training of pharmacists in the preparation of CVMs and the absence of any accreditation of pharmacists in the quality of CVMs are fundamental deficiencies that the AVA is endeavouring to address.

Precision veterinary medicine

With regard to pharmaceuticals, precision medicine consists of four key elements:

1. Right diagnosis
2. Right drug
3. Right time
4. Right dose

Access to veterinary medicines and use guided by the refinements provided by the progressive availability of real-world evidence are fundamental elements of precision medicine – right diagnosis, right drug, right time, right dose. The benefits and desirability of precision medicine are keenly sought in both human medicine (Dahabreh et al. 2016; Dugger et al. 2018; Hunter and Longo 2019; McColl et al. 2019; Peck 2016; Peck 2018; Percha et al. 2019; Rawson et al. 2018) and veterinary medicine (Almela and Bäumer 2017; Buckley and Lyons 2020; Gray et al. 2018; Katogiritis and Khanna 2019; Klopfleisch 2015; Lloyd et al. 2016; and Pang and Argyle 2016) and precision medicine will occupy a prominent place in veterinary medicine well into the future.

Efficacy, Effectiveness, Efficiency

Precision medicine relies on effectiveness, but what does this mean?

The important distinction between efficacy and effectiveness has been described in an Editorial in the BMJ (Haynes 1999) where it is acknowledged that the British pioneer clinical epidemiologist Archie Cochrane defined efficacy as the extent to which an intervention does more good than harm under ideal circumstances ("Can it work?") and effectiveness as the assessment as to whether an intervention does more good than harm when provided under usual circumstances of medical practice ("Does it work in practice?"). It is well known in veterinary practice that determining the best treatment for an individual (the task of the veterinarian – effectiveness assessment) is fundamentally different from determining the average effect of treatment in a population (the purpose of a trial - efficacy). The concept of heterogeneity of treatment effects (Dahabreh et al. 2016) is essential in providing the evidence base for precision medicine and patient-centred care as there are inherent limitations of using group data (efficacy data for example provided by a randomized trial) to guide treatment decisions for individual patients (where prediction of effectiveness is the key requirement).

Real World Data and Real World Evidence

There has been growing interest in the use of Real World Data (RWD) and Real World Evidence (RWE) to monitor and assess effectiveness and the US Center for Veterinary Medicine (CVM 2020c) has recently released a guidance document that defines real-world data and real-world evidence as follows:

Real-World Data (RWD) are data collected from a variety of sources relating to the health and productivity of animals, the delivery of veterinary care, or the management of livestock/animals for food.

Examples of RWD applicable to veterinary medicines include:

- Data derived from health records of veterinary practices, farms, or livestock management companies (including handwritten paper records and electronic veterinary medical records;
- Data from product and disease registries;

- Data from other sources that can inform on animal health status such as mobile and/or remote health sensing devices for animals;
- Data generated by animal owners;
- Data from diagnostic laboratory, slaughterhouse, and abattoir records;
- Companion animal and livestock insurance claims (for example, Hardefeldt et al 2018;a Wolf et al 2020); and
- Data from surveillance programs.

Real-World Evidence (RWE) is the clinical evidence of the effectiveness of a new veterinary medicine derived from analysis of RWD.

Because RWD are collected as part of the routine care and management of animals, including their health and/or productivity, these data may be useful to support effectiveness and safety (contributing to pharmacovigilance) of a drug in a diverse population of animals and conditions of use.

The potential use of various RWD sources to generate RWE to support assessment of effectiveness and safety or reasonable expectation of effectiveness is dependent on:

- Selection of data sources that appropriately address the study question and sufficiently capture representative study populations, exposure, outcomes of interest, and key covariates (RWD relevance);
- RWD quality; and
- Design and analysis of studies utilizing RWD to generate RWE.

Because of the importance of effectiveness and safety of human (and veterinary) medicines the collection of RWD and the translation to RWE has received considerable attention (Bartlett et al. 2019; Basch and Schrag 2019; Beaulieu-Jones et al. 2020; Bolislis et al. 2020; Breckenridge et al. 2019; Brouillette 2020; Corrigan-Curay et al. 2018; de Lusignan et al. 2015; ElZarrad and Corrigan-Curay 2019; Franklin et al. 2020; Jarow et al. 2017; Keizer et al. 2020; Lamberti et al. 2018; Lasky et al. 2020; Miksad et al. 2019; Oehrlein et al. 2018; Patorno et al. 2020; Ramagopalan et al. 2020; Ramamoorthy and Huang 2019; Rivera et al 2019; Scoble, et al. 2020; Seifu et al. 2020; Sherman et al. 2016; Snyder et al. 2020; Spitzer et al. 2018; Swift et al. 2018; Tyczynski and Kilpatrick 2019; Wang et al. 2020; Wu et al. 2020; Yuan et al. 2018).

To identify new indications for established medicines and to capture experiences of better use of existing medicines the FDA has established a website where RWD from experiences in human medical practice can be posted for later analysis (FDA and NCATS 2020). A similar approach of collecting information could be very beneficial in veterinary medicine.

A highly valuable source of RWD is that provided by the clinical records of individual patients.

The General Practice Research Database (GPRD) is a well-established and productive (almost 1,000 research publications have been generated) example of a UK human Primary Care Data resource (Williams et al. 2012; Wood and Martinez 2004) that allows rich mining of copious data. However, the use of veterinary clinical records to improve decision making and enhance the use of veterinary medicines is a more recent and rapidly expanding field that can be expected to transform and refine current and future veterinary practice (Awaysheh et al. 2019; Faunt et al. 2007; Glickman et al. 2005;

Glickman et al. 2006; Guevara et al. 2019; Hale et al. 2019; Hur et al. 2019; Hur et al. 2020; Jones-Diette et al. 2016; Jones-Diette et al. 2017; Jones-Diette et al. 2019; Kass et al. 2016; Lund 2015; McGreevy et al. 2017; Moore et al. 2007; Moore, et al. 2005a; Moore, et al. 2005b; Muellner et al. 2016; Nelson et al. 2017; Radford et al. 2011; Sanchez-Vizcaino et al. 2015; Schofield et al. 2020; Vandeweerd 2019; and Yao et al. 2015).

The Banfield Pet Hospital national computerized record system in the US (for example, Glickman et al. 2006), SAVSNET, the small animal veterinary surveillance network (Radford et al. 2011 and Sanchez-Vizcaino et al. 2015) and VetCompass (Hur et al. 2019; Hur et al. 2020; McGreevy et al. 2017; and Schofield et al. 2020) each provide numerous examples of collecting RWD and converting it to RWE to guide improvements in veterinary practice. Concerns at the safety of vaccination of dogs and cats or the use of a particular heartworm preventive medicine have all been examined by the use of RWD and RWE (Glickman et al. 2005; Moore et al. 2007; Moore, et al. 2005a; Moore, et al. 2005b; and Yao et al. 2015), with concerns allayed on the basis of the practical experience revealed by examination of clinical records.

Other significant responsibilities of the veterinary profession

Animal welfare

Veterinarians are committed to the health and welfare of animals, with ethical, legal and professional responsibilities (for example, Salvin et al 2020). When selecting and using a veterinary medicine the welfare implications are always included in the assessment of the balance of benefits and risks.

Pain management is a significant undertaking of veterinarians with avoidance or minimisation of pain is preferred but the use of analgesic veterinary medicines is a growing requirement.

Emerging infectious diseases

The seminal publication by Jones et al (2008) on global trends in emerging infectious diseases (EID) reviewed what was already known but highlighted the significant burden of EID on global economies and public health. Furthermore, the review founds that 60% of EIDs had an animal origin (ie they were zoonotic) and that 72% of these zoonotic diseases originated in wildlife, and it was reaffirmed by other authors (Watanabe 2008) that wildlife may be the source of the next pandemic. The current coronavirus pandemic is a stark reminder of the truth of these predictions. There is considerable attention applied to EID (for example, Allen et al 2017; Bueno-Marí et al 2015; Carroll et al 2018; Cutler et al 2010; Halliday et al 2017; Kruse et al 2004; Le Turnier et al 2020; Machalaba and Karesh 2017; Ogden et al 2017; Plowright et al 2019; Scott et al 2020; Thompson and Kutz 2019) with the veterinary profession playing a central role. However, collaborative and cross disciplinary approaches are essential, providing renewed relevance and attention to the concept of One Health.

One Health

The One Health Commission defines One Health as a "collaborative, multisectoral, and trans-disciplinary approach - working at local, regional, national, and global levels - to achieve optimal health and well-being outcomes recognizing the interconnections between people, animals, plants and their shared environment" (https://www.onehealthcommission.org/en/why_one_health/what_is_one_health/). In the context of EID and AMR, the veterinary profession expends considerable resources and has gained significant expertise in one health (Barnett et al 2020; Connolly 2020; Franco-Martínez et al 2020; Harrison et al 2020; Hemida and Ba Abduallah 2020; Humboldt-Dachroeden et al 2020; Jenkins et al 2015; Leroy et

al 2020; Lustgarten et al 2020; Mackenzie and Jeggo 2019; Narrod et al 2012; One Health Initiative Task Force 2008; Overgaauw et al 2020). When veterinary medicines (pharmaceutical and vaccines) are required to contain an EID or to reduce the likelihood of AMR, a facilitating and cooperative regulatory environment is essential.

Antimicrobial resistance and stewardship

The AVA has been actively involved in fighting the emergence of antimicrobial resistance for more than 30 years with the development of guidelines, codes of practice and policies (https://www.ava.com.au/library-resources/other-resources/fighting-antimicrobial-resistance/).

The AVA work closely with the medical community to address the intersecting issues of antimicrobial resistance. The AVA is represented on the Australian Strategic and Technical Advisory Group on AMR (ASTAG) which has developed importance ratings of antibacterial agents used in human and animal health in Australia (ASTAG 2018). The recommendations of ASTAG are reflected in the prescribing guidelines and antimicrobial stewardship plans implemented in veterinary practice.

The AVA has published comprehensive guidance on prescribing and dispensing of veterinary medicines (AVA 2005), including antimicrobial agents, and the use of antimicrobials in veterinary practice has been the subject of a number of published surveys (Hardefeldt et al 2017, 2018a; Badger et al 2020), the results of which guide continuous improvement discussions and actions.

The veterinary profession in Australia has worked closely with all areas of animal health to develop the principles of antimicrobial stewardship (AMS) (Weese et al 2013; Lloyd and Page 2018) and AMS programmes for the chicken meat industry (Alfirevich 2019), pork industry (van Breda et al 2019), dairy cattle (Coombe et al 2019), feedlot cattle (Badger et al 2020), and horses (Raidal 2019). Supporting the species specific AMS programmes has been the development and introduction of antimicrobial prescribing guidelines for pigs (Cutler et al 2020) and poultry (Gray et al 2020) with other guidelines in the process of development (https://www.ava.com.au/library-resources/other-resources/fighting-antimicrobial-resistance/). Further support has been provided by an online AMS training (Norris et al 2019) and the recent First Australian Veterinary AMS conference (AVAMS18 2018), with a second conference originally planned for 2020, but now rescheduled (as a result of the current pandemic) for 2021.

Other resistance issues

Managing resistance to ecto- and endo-parasiticides is a major challenge is some regions and/or sheep/goat and other livestock enterprises. Such resistance is often an unrecognised limit to productivity and/or cause of compromised animal health and welfare. For some sheep enterprises, this represents the need for the most critical input by veterinarians.

Conclusion

The practice of veterinary medicine is becoming more specialised and sophisticated as new technologies become available to help detect and diagnose disease and as new treatments become available to manage the health and welfare of veterinary patients.

Access to high quality medicines and continual monitoring of effectiveness and safety will remain core elements of veterinary practice in the future.

The veterinary profession is constantly adopting new approaches to refine and perfect its approach to precision medicine. Working closely within a regulatory environment that facilities and supports

the evolution of the profession and its practices will ensure that owners and their animals receive the best possible treatment.

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Agvet Review Introduction

PROPOSED VISION STATEMENT

The proposed 'vision statement' for the system that the panel is inclined towards is:

An Australian regulatory system for agvet chemicals that provides all Australian primary producers and veterinarians with timely access to a similar range of approved agvet chemicals to their overseas competitors, while preserving human, animal, plant, and environmental health.

1) Do you support the proposed vision for the agvet chemicals regulatory system and is it sufficient to meet the needs of all stakeholders?

    a) What, if any other considerations should be included in the vision?

Do you have any suggestions for reforms that could assist in achieving this vision that are not canvassed in this paper?

DISCUSSION

The vision statement should also include the promotion and facilitation of innovation and recognise the importance of veterinary medicines that are developed in Australia.

Chapter 1: is the national registration scheme working as needed?

1.1 State of the system

Discussion questions

2) Do you agree or disagree with the future trends identified and their implications for the agvet chemicals regulatory system?

   a) Are there additional implications for the regulatory system posed by the trends identified that the panel has not adequately addressed? If yes, please provide details.

   b) Are there other trends that the panel needs to consider in designing the future system?

DISCUSSION

Further to the summary of veterinary practice in the introduction, there is a well-established and clear trend for greater growth of companion animal veterinary medicines in terms of innovation and sales. It is expected that technologies increasing influencing human medicine (for example 3D printing [Bhat 2021]) will increasing lead to innovations in the development and availability of veterinary medicines.

Many new biological technologies are being developed, including (but of course not limited to) greater focus on the therapeutic use of monoclonal antibodies, CRISPr, micro RNA, and other gene therapies.

As consolidation of the veterinary medicines industry continues and as costs of product development, registration and supply increase, there is a growing need to consider the security of supply of veterinary medicines, especially for the vast number that are only manufactured outside Australia and imported for use.

It should be recognised that the veterinary profession as a whole is the repository of vast experience, expertise and practical knowledge of the medicine of animals and the diagnosis of disease. The regulator has special knowledge of regulatory science. The combination of these varied and complementary skill sets seems an obvious forum for ongoing collaboration and cooperation.

1.2 What should be the core objectives of the future system?

Proposed primary purpose statement

The panel would welcome feedback on the primary purpose statement of the system being:

The purpose of the agvet chemicals regulatory system is to protect the health and safety of people, animals, plants and the environment and provide safe and timely access to agvet chemicals.

It does this by preventing or managing unintended adverse consequences from exposure to agvet chemicals in food, the environment, and the workplace; and by ensuring that suitable pest management solutions are available to safely control the pests and diseases of plants, animals, and places, that threaten the health and safety of people, animals, plants and the environment.

The panel's proposed hierarchy of objectives.

Discussion questions

3) Do you support the proposed overarching primary purpose statement for the agvet chemicals regulatory system being safety and access?

   a) Do you agree that the proposed hierarchy of simplified objectives provides greater clarity of their relative importance and is this supported? If not, why?

   b) Are there objections to removing the domestic chemical manufacturing objective? If so, what are the objections?

   c) Do you agree that the current objectives for efficiency, transparency and risk-based science are more appropriately expressed as principles governing design of the system? If not, why?

   d) Are there other objectives that should be considered?

DISCUSSION

Rather than a hierarchy, each of the objectives should be on the same level as they do not all apply in every situation – notably products for companion animal and other non-food animal species have no interaction with primary production or trade.

Removal of the domestic chemical manufacturing objective can be very short sighted. It seems to assume that local manufacture has not significantly contributed to the innovation currently available to the animal health industry. However, while new innovations usually arise from larger companies, Australia has a strong record of local companies leading innovation delivery to the end user.

Perhaps a more visionary perspective could be – how can regulatory legislation be amended to facilitate the ability of companies (including startups) to move into the innovation spaces left by the continued merger of large companies. The small global size of the Australian industry doesn't support significant innovation spend for Australian specific projects and it is often only where companies have retained a local, focused R&D centre with committed funding for the region that innovative products for Australian unmet needs are developed and introduced.

The issue of domestic food security is sufficiently important to be considered. In view of the range of zoonotic diseases of animals, protection of the HEALTH and welfare of animals is important (for example, not all zoonotic diseases cause welfare problems in the host animal).

1.3 What principles should underpin design of the system?

Discussion questions

4) Do you support the principles proposed to guide design and reforms to the future agvet chemicals regulatory system? If not, why?

   a) How could these principles be enshrined to ensure they are met?

   b) Do you have suggestions for additional principles that should be considered by the panel?

DISCUSSION

Effectiveness assessment of each selected new measure is a principle that should be considered

1.4 Is a risk-based system better than a hazard-based system?

Panel's view

The panel is of the view that it is critically important that Australia's future regulatory system is based on risk, not hazard alone. Such an approach provides for a more scientifically robust and comprehensive regulatory system, and incorporates hazard assessments along with exposure and use, to determine chemicals suitable for use and the safest way of using them. This approach also ensures that users and the community have access to the broadest suite possible of safe chemicals to manage pests and diseases.

Discussion question

5) Do you agree that the regulatory system needs to have a risk-based focus to provide for a more scientifically robust and comprehensive system? If not, why?

DISCUSSION

A rigorous, transparent, objective and scientific risk-based approach to the evaluation of veterinary medicines is supported. Clear risk questions that define the risks under assessment are an important starting point and should always be explicitly stated.

Risks can be fluid, especially as exposure situations change. How will the system adjust to new information that is relevant to the assessment of risk?

It is appreciated that risk management is a separate but complementary discipline and inherent component of the three arms of risk analysis (risk, management and communication). Some clarity on how the outcome of a risk assessment is converted to a regulatory decision would be very valuable.

Chapter 2: who should ultimately be responsible for aspects of the system?

2.1 How should the supply of agvet chemicals be regulated?

Panel's view

The panel has a strong view that there is little justification for considering any changes to the current approach of a single national regulator for the supply of agvet chemicals.

2.2 Who should lead key responsibilities and reforms for the national system?

Discussion question

6) What governance structure might be best for delivering the Australian Government's responsibilities in the national regulatory system?

   Do you see merit in a time-limited High-Level Steering Committee to drive implementation action on the regulatory reform agenda?

DISCUSSION

The governance structure that is most desirable consults with stakeholders, seeks guidance from within and beyond when addressing complex issues, appreciates the separate but related importance of science based risk assessment and socially and environmentally responsible risk management, retains scientific vigour, is consistent in decision making while being flexible. Option 2, statutory authority with board, may most closely reflect these features.

Implementation of reforms is essential, and merit is seen in having a high-level steering committee responsible for ensuring effective and efficient implementation – as judged by independent and transparent ongoing intra- and post-implementation assessment.

As evident from recent government enquiries, the chain of command is critical, and a clear governance and organisational structure is critical.

2.3 Should control of use be nationally consistent?

Option 1 Expanded applied law model

Option 2 Commonwealth exercising its full constitutional reach

Option 3 Re-invigorating the existing Intergovernmental Agreement on control of use

Discussion questions

7) Which of the three reform options outlined do you support and why?

   a) Which option is likely to deliver the best chance of consistency in control of use and the greatest likelihood of success and why?

   b) What risks do you foresee in implementing any of the options proposed?

DISCUSSION

The AVA fully supports national harmonisation of veterinary medicine use, veterinary prescribing rights and national coordination of domestic produce residue monitoring. Option 1 (expanded applied law model) is considered likely to deliver the long-overdue national consistency that has long been sought. As veterinarians operate across State borders, a consistent approach is fully supported. Harmonisation of use should also allow one veterinarian to supply another veterinarian with veterinary medicines needed to support the health and welfare of animals, especially in cases of stock-outs or unavailability of the essential medicines. For harmonisation, no risks, only benefits, are foreseen in a veterinary context.

2.4 Should there be shared responsibilities between industry and government?

Discussion questions

8) Do you support the addition of co-and-self regulatory approaches to agvet chemicals management (across all levels of a product lifecycle like the Australian Packaging Covenant) to deliver more effective and efficient outcomes than direct regulation alone?

   a) Do you support the panel's proposal for a holder accreditation scheme? Would the proposed levels of accreditation provide greater incentives for industry compliance?

   b) Is there additional value in limiting the scope for a holder based on the nature of the registration?

   c) Do you agree with the panel's proposal for formal training requirements for users to access (purchase) agricultural chemicals above a certain volume?

   d) Do you have suggestions for how existing assurance schemes such as GMP could be used to streamline assessment processes?

   e) Is there value in a statutory duty of care on industry and/or users to strengthen incentives for responsible use of chemical products to minimise risks to human health, animals and the environment?

   f) Can you think of any alternative or additional measures the government could implement to strengthen the responsibilities of regulated entities and users?

DISCUSSION

There already exists a shared responsibility between government and the veterinary profession. Veterinarians have completed comprehensive training and education in all clinical aspects of veterinary medicine, including the examination of animals, diagnosis of disease, selection and use of veterinary medicines and ongoing monitoring of the response of each treated animal to treatment. Veterinarians have a number ethical and legal responsibilities pertaining to the use of veterinary medicines. The shared responsibility must continue for the benefit of the health and welfare of animals. Government should recognise the role of individual veterinarians in supporting animal health and welfare and in addition to a shared responsibility, there should be consultation, collaboration and cooperation on the development of new veterinary medicines and facilitation of their refined use as new information becomes available.

2.5 Is compliance and enforcement effective?

Panel's view

The panel notes that state and territory regulatory powers to control agricultural chemical and veterinary medicine use differ from jurisdiction to jurisdiction, as does the approach to compliance by the various regulators. The panel is inclined to recommend a national approach to compliance and enforcement of agvet chemicals use that employs a consistent set of compliance and enforcement tools. For example, there could be a more consistent approach to: licensing of chemical users; monitoring and investigative powers; record-keeping requirements; and the full suite of administrative actions, plus civil and criminal penalty provisions with a consistent range of available sanctions.

Discussion questions

9) Should detection and investigation measures be augmented to better treat the risks posed by agvet chemicals?

   a) Do agvet chemicals regulators need more effective and nationally consistent tools and sanctions than they already possess to manage the risks for which they are responsible?

   b) Do agvet chemicals regulators have appropriate resources, appetite and/or incentive to use the detection and enforcement tools they have? If not, how could this be addressed?

   c) Are you confident that regulators will detect non-compliance (in particular, that which poses the greatest threats to human and animal health and the environment) and respond appropriately? If not, what should/could be done differently?

   d) Should agvet chemicals registration-holders be screened in some way to ensure they are reputable? Why, why not?

DISCUSSION

In general, the existing compliance and enforcement measures work well, with the addition of Veterinary Practitioner Boards in each State available to act on complaints as well as regularly reviewing competence of veterinarians and standards of veterinary hospitals. The current system of compliance relies on reports of complaints. A system that was progressive and supportive and that included random audits could improve compliance and reduce the need for enforcement.

Chapter 3: what chemicals are currently regulated?

3.1 Should the system only include chemicals for primary producers, veterinarians and non-urban land managers?

Panel's view

The panel is disposed to removing from the scope of the agvet chemicals regulatory system products with limited relevance to primary production or animal welfare. As examples this would include most consumer goods, pool and spa chemicals, antifouling paints and some veterinary products.

The panel considers that this would give a clearer 'identity' to the agvet chemicals regulatory system: it supports Australian primary production, veterinarians, and non-urban land management.

The panel is also disposed towards the introduction of restrictions of 'veterinary use only', where warranted for animal welfare, along similar lines to that adopted for agricultural chemicals currently under the auspices of Restricted Chemical Products. The panel considers that at the minimum, and to the extent not already addressed through scheduling, injectable veterinary products should require the direct involvement (either in administration or under their instruction) of a veterinarian.

Discussion questions

10) Do you support the proposal to remove consumer products and pool and spa chemicals, anti-fouling paints and certain over-the-counter companion animal products from the agvet chemicals regulatory system? If not, why?

    a) Do the benefits of the proposed removal of these products outweigh the risks? If not, why?

    b) Are the new definitions of a plant protection product and veterinary medicine supported? If not, why?

    c) Do you agree that certain product uses, such as those administered by injection, warrant the direct involvement of veterinarians, separate to the controls under the poisons scheduling?

DISCUSSION

Re the following examples, apply risk assessment approaches (eg flea collars) and consider limitation of claims.

- many over-the-counter companion animal products, in particular impregnated material (such as flea collars)
- most products based on essential oils or other herbal extracts
- products containing only substances generally recognised as safe (GRAS), set out in regulation

The animal welfare implications of removing the products currently regulated needs to be considered. For example, effective parasite control is important from an animal welfare and often from a public health perspective. Effective parasite control can only be achieved by those acting on the basis of the epidemiology, population dynamics and resistance status of the target parasite.

With clear guidance on use, parasite resistance selection is hastened and the availability of effective antiparasitic veterinary medicines reduced. The emergence and dissemination of flea, tick and helminth resistance to existing veterinary antiparasitic classes is becoming a critical issue as new classes are not being developed at a pace to replace the current classes.

When considering the removal of products from the requirements of registration a thorough risk assessment should be completed. As risks are likely to change with time it is important that a system of monitoring excluded products is introduced. Currently, products excluded from use are not the subject of any list or register, they remain unknown to the regulator. This is not necessarily a good thing. For example, probiotics are excluded from the requirements of registration if they meet a number of self-assessed tests. If the manufacturer is satisfied that the tests are met, then the product can be manufactured, sold and used without any knowledge of the regulator. If a problem emerges it may be completely hidden from view. For example, probiotic products can be exempt from registration. However, there is considerable literature that has found that probiotic bacteria can have a variety of acquired antimicrobial resistance determinants that can be disseminated to treated animals (Ben Braïek and Smaoui 2019; Brodmann et al 2017; Castro-González et al 2019; Das et al 2020; de Melo Pereira et al 2018; Jeżewska-Frąckowiak et al 2018; Kothari et al 2019; Lee et al 2019.; Li et al 2020; Selvin et al 2020; Sharma et al 2014; Sharma et al 2016; Wang et al 2020). Thus, antimicrobial resistance could be widely distributed by an exempt product with no oversight. The need for risk assessment and ongoing monitoring is essential.

There is a concern that ineffective herbal anthelmintics are permitted to be sold in some countries such as the USA. Goats are particularly susceptible to helminthoses, and deaths have resulted from use of these products – therefore, risk assessment very important.

3.2 Should agricultural and veterinary chemicals be regulated together?

Discussion questions

11) Are there areas where the approach to agricultural chemicals and veterinary medicines should be different?

    a) Should there be separate requirements specified in the legislation for veterinary medicines and agricultural chemicals? If so, what should these requirements be?

DISCUSSION

The introduction to this submission highlights many of the differences. To summarise, there is often an important distinction in use patterns between products for food producing animals and for other animal species (dogs, cats, horses, birds, fish, zoo, fauna, exotic etc)

Veterinarians who select and prescribe veterinary medicines are highly trained to undertake a challenging professional role in the diagnosis and treatment of disease and dysfunction and maintain animal welfare. As practicing veterinarians, they have obligations to maintain continuing professional development.

Greatest risk of use of a veterinary medicine is generally to the patient and not the owner.

Individualisation of treatment is important for many companion animal products.

This underpins the need for efficacy assessment as safety is dependent on dose selected for use and other aspects of the dosage regimen (for example single or short term use or long term even lifetime use). Unlike in the agchem world, in small animal medicine many veterinary medicines are

administered repeatedly for life, for example, daily doses of insulin in diabetic animals, daily doses of non-steroidal anti-inflammatory drugs for animals with osteoarthritis, daily doses of cardioactive drugs for animals with heart disease. There are a multitude of other examples.

Restraint statements (DO NOT USE) in labels are a particular problem in veterinary medicine prescribing and use. There is a substantial view that these should only be included when there is a specific risk, rather than as a default if data (eg on milk WHP) has not been provided (to save cost) by the registrant.

Chapter 4: are there gaps in agvet chemicals regulation or management?

4.1 Can we assess use by region, pest, disease or other instead of state boundaries?

Discussion questions

12) What are the merits of considering boundaries (other than state) that might be relevant to the use patterns of agvet chemicals use?

    a) What are the merits of considering regions of significant environmental interest, such as those adjacent to the Great Barrier Reef, or unique environmental values, for restrictions or bans on some agvet chemicals uses?

    b) What are the merits of mandating five yearly label reviews (by the holder) to remove where appropriate state references and aligning with the review of safety data sheets?

    c) Is it possible to establish pest groupings?

DISCUSSION

For most veterinary medicines use is similar nationally. There are some exceptions where particular diseases or intoxications are present in restricted areas. For example, tick paralysis due to envenomation by *Ixodes holocyclus* is restricted to the east coast of Australia. Arthropod borne diseases are restricted by the occurrence of the vector. Diseases like Johne's Disease of sheep and cattle and virulent footrot of sheep may be subject to specific disease management zones.

4.2 Should benefits be considered in assessments?

Discussion questions

13) Would a benefits test as proposed be a useful addition to the agvet chemicals regulatory system?

    a) Are the benefits outlined appropriate?

    b) Are there additional benefits that should be considered?

    c) Should the benefits test have the two purposes proposed?

DISCUSSION

A benefits test could reasonably be applied to veterinary medicines. For example, in the control of rabbits the chemical and biological approaches currently available are far from meeting even a low standard of animal welfare. If a new veterinary medicine became available that had demonstrable improvement in animal welfare then it should qualify for a benefits assessment and expedited review. Similarly, if an antibacterial veterinary medicine became available that did not select for antimicrobial resistance of public health importance, it can be the subject of a benefits test.

Related to the benefits tests described in the issues paper are the various types of expedited review that are available under the US FDA Expedited Development and Review Pathways (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics), including Fast Track-designated drugs that have

the potential to address unmet medical needs; breakthrough therapies that apply to drugs for serious or life-threatening diseases for which there is unmet medical need and for which there is preliminary clinical evidence demonstrating that the drug may result in substantial improvement on a clinically significant endpoint; and Priority Review if the FDA determines that the drug could potentially provide a significant advance in medical care. To promote innovation in veterinary medicine development, such expedited pathways would offer some encouragement.

There are many unmet needs in veterinary practice and measures designed to encourage and facilitate the introduction of new products to satisfy these needs are highly important. One very pertinent example relates to the enhancement of chicken welfare where there are no analgesic products registered for use. The market for such products is insufficiently large to offset and justify the cost of development and registration. However, mitigating pain and improving welfare are such important objectives. Any measures that the regulatory system can apply to allow significant gaps (such as this example provides) to be overcome is highly desirable.

4.3 Should the impact of chemical combinations matter?

Discussion questions

14) Is the area of chemical combinations highlighted worth exploring?

   a) How might consideration of the impacts of chemicals (cumulative and synergistic) be feasibly considered in the Australian system, given the limited progress in this area internationally?

   b) Should Australia wait until international methodologies for assessing impacts of chemical combinations have been developed? Or should Australia have a role in assisting in their development?

   c) What skills and tools are needed in Australia to allow consideration of the impacts of synergistic impacts of chemicals?

DISCUSSION

This is a complex field. The US and EU approach focuses on areas that the APVMA already manages through controls such as personal exposure limits, application rates, frequency of use patterns, withholding periods as some examples.

The biological value of combination use is an area that lacks substance and structure in a review process and in fact across the animal health space. This is more evident in the ectoparasiticide area as the endoparasitic area seems to have aligned clearly around the use of combinations. However, there is a role for veterinarians with specific expertise in management of both endo and ectoparasitic infestations under different management systems to assist the regulators develop an appropriate review process. In the case of ectoparasiticide management of production animals, best practice use of combination is less clearly defined.

4.4 Can data mining drive better targeting of effort?

Panel's view

The panel acknowledges these issues would need to be addressed in the implementation of any relevant initiative. If governments are to achieve the benefits that data mining offers it will be essential for them to find a way of enabling access while protecting intellectual property and privacy.

Nevertheless, the panel sees considerable potential in more effective data mining arrangements in the regulatory scheme of the future.

Discussion questions

15) What role could data mining and intelligence use play in the regulatory system?

    a) Should governments improve their data holdings and share this data among the jurisdictions to improve the management of agvet chemicals?

    b) Should agvet chemical users be required to mandatorily report chemical use data to the regulator? On what basis, If not, why?

    c) How could data mining and analytics drive better targeting of regulatory effort?

    d) What standards should operate to ensure data integrity, confidentiality and use?

DISCUSSION

Reporting of the use of veterinary medicines has many benefits, however, registrants can only report sales data and quantities of active constituent used in manufacture of veterinary meidcines, not how the product was ultimately used. A system of clinical record review and audit to determine actual use that was anonymised and non-threatening could provide valuable ongoing real time information. This approach is considered in greater detail in the introduction where the growing recognition of real world data and real world evidence is discussed.

Australia has some global responsibilities for reporting, for example antimicrobial use and resistance to OIE.

4.5 Should there be greater monitoring of chemicals in produce and the environment?

Discussion questions

16) Do you support the need for a national domestic produce monitoring system and should it be modelled on the National Residue Survey?

    a) Should data on residues in domestic produce be publicly available?

    b) What should core design principles of such a system encompass?

DISCUSSION

As suggested earlier in this submission, a residue monitoring programme that provided information that could guide extra label use (ELU) would be invaluable. In food production practice there is frequently a need to vary label dose information. For pathogens subject to changes in susceptibility due to resistance selection, the label dose is usually inadequate (for example, see the important publication of Hardefeldt et al 2018b). Appropriate treatment then relies on modifying the dosage regimen. As this invariably has residue implications (which the prescribing veterinarian review and manages by determining and recommending an appropriate withholding period (WHP)) it would be valuable to know if the amended WHP allows the tissue residues to deplete below the maximum residue limit (MRL).

Discussion questions

17) How could consistency in water and environmental monitoring across jurisdictions be achieved?

    a) Would monitoring systems (for both water and the environment) based on risk priorities be effective?

    b) Are there specific environments that should be a priority for monitoring?

Should monitoring results be published and how often?

DISCUSSION

As part of an overall One Heath approach (summarised in the introduction) it is valuable and beneficial to undertake environmental monitoring and surveillance, which should include the presence and type of antimicrobial resistance determinants.

There is support for data to be published, similar to NRS reports. However, there may be a need for exemptions such as for data from investigations being undertaken to establish new methodologies.

Chapter 5: how can communication and engagement be improved?

5.1 Is there a need for more community information on regulatory actions?

Discussion questions

18) What information would consumers like to see more of from the national and state agvet chemicals regulators?

    a) How would consumers prefer to receive information?

    b) What should be the role of regulators in communicating decisions to the wider community?

DISCUSSION

Should the APVMA engage in community education or could another government group do that – it is important to try to manage the false and misleading information spread by groups with ulterior motives. The AVA could play a critical role here as having the national regulator play a more forward thinking role in educating the community could be impactful. The AVA have a community perspective and communication outreach that could greatly facilitate this strategy. The strategy could be based on the APVMA/AVA openly supporting the continued access to innovation for the benefit of the community with a program of consumer appropriate education topics. This could represent another element in a collaborative and cooperative forum of regulator and veterinary profession. Interestingly and perhaps surprisingly, awareness of the APVMA within the veterinary profession (especially those in practice) is (anecdotally – as no formal survey has been undertaken) very low.

5.2 Do stakeholders require a formal consultation mechanism with the regulators?

Panel's view

The panel is disposed towards a consultative mechanism, like the UK model, with active functions that give it momentum and a greater likelihood of being sustained over time.

Discussion questions

19) Do you support the establishment of a formal consultative forum in Australia, similar to the UK model? If not, why?

    a) Do you have suggestions on the possible membership and scope for a formal consultative forum in Australia?

    b) If this model is adopted would there be benefits in forum meetings being open to the public?

DISCUSSION

Consultation with the community is essential. As veterinary medicines address a large expanse of medical need there is also a need for a consultative forum with the veterinary profession. This veterinary medical consultative process should be an ongoing process that reviews acquired

experience with current products (an expanded pharmacovigilance programme that looks at safety, efficacy and new product applications) as well as provides professional input on unmet needs, innovations and other subjects of mutual interest.

There are concerns about the loss of key personnel with the relevant expertise and experience. Addressing this deficiency requires prioritisation.

Chapter 6: how can we simplify the regulatory system?

6.1 Does a product that is the same as another need its own assessment?

Option 1: Repack applications become a declaration/notification process

Option 2: Link the registration status of repacked products to the pioneer product

Option 3: Continue to assess repack applications as per the current approach

Discussion questions

20) Which of the three repack application options presented do you prefer and why?

   a) Are there likely to be any increased risks with a product if option 1 is adopted?

   b) In option 2, is it reasonable to cancel the registration of all repacks following cancellation of the pioneer product (except in circumstances where the registration holder is in possession of appropriate data and product information)?

   c) Are there alternative options for dealing with repack applications?

DISCUSSION

Repacks are a special case and can reasonably be expected to be the same as the pioneer product

AVA supports option 1, this allows for the APVMA to minimise the regulatory burden, further it allows for ongoing access to products if the pioneer product ceases to be available. As the formulation owner needs to approve the application this ensures products are not copied without approval from the formulation owner.

Option 2 – not supported as there is a risk that the original formulation owner cannot be contacted and all versions of the product are unregistered despite ongoing demand.

6.2 Who should be responsible for ensuring products work?

Option 1: Removing efficacy from the scope of agvet chemicals regulation

Option 2: Removing the requirement for efficacy data assessment

Option 3: Maintaining the criterion and amending requirements and streamlining assessments

Discussion questions

21) Which of the three options presented for retaining (for specific products), reducing or removing efficacy from the current agvet chemicals regulatory system do you prefer and why?

   a) Do you support applying option 1 to all crop protection products and non-scheduled veterinary medicines? If not, why?

   b) Do you support applying option 2 to scheduled veterinary medicines? If not, why?

   c) Are there unmanageable risks or costs if the efficacy criterion was removed or reduced from the regulatory system? If so, could you provide details?

DISCUSSION

This subject is explored in some detail in the introduction to this submission. The important distinction between efficacy and effectiveness is highlighted as are the advantages of collection and analysis of real world data and converting it to real world evidence.

The principles of risk assessment should apply here. In many cases, for example veterinary medicines used chronically or for a lifetime (as is increasingly the case in non-production animal practice) there will be many adverse consequences if the product is found to be ineffective and efficacy studies should be undertaken to demonstrate the product is effective before registration.

Similarly, for vaccines and other preventative products such as those used for various CNS, cardiovascular, dermatological, immunological and other disorders. Imagine a Hendra virus vaccine that was ineffective? Or if vaccination of dairy cattle against leptospirosis was not effective and the dairy farmer and his workers were exposed and developed leptospirosis.

There is a continuum of efficacy needs and the risks need to be determined and efficacy requirements elucidated.

VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) have international guidelines for efficacy assessment (https://www.vichsec.org/en/).

For companion animals the risks of inefficacy can be very high. There are similarities in considering human paediatric medicines and those for companion animals.

The AVA strongly supports Option 3, many of our members particularly those who work in the Veterinary Pharmaceuticals Industry have a range of concerns in relation to Options 1 and 2. Approving veterinary chemicals without review of the efficacy represents poor science and poses risks to animal welfare which is a core tenet of the AVA. There is no effective system through existing consumer laws to protect against ineffective veterinary products. Regulatory authorities in both Europe and the USA have extensive Industry guidance documents in relation to minimum efficacy requirements to ensure product efficacy. Some key examples are the requirement of >95% efficacy for tick products as there is a significant likelihood of death from ticks (for example the paralysis tick, *Ixodes holocyclus*) if ineffective products are approved. Treatment of broilers with anticoccidial agents that were not effective could readily lead to the death of thousands of birds. The World Association for the Advancement of Veterinary Parasitology (https://www.waavp.org/) has produced guidelines for the efficacy of parasiticides for large and small animals which need to be followed for registration in Australia, NZ, EU and the USA. In addition, the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) (https://www.vichsec.org/en/) has produced a series of guidelines for pharmaceuticals and biologicals for Good Clinical Practice (GCP), Anthelmintics, and Bioequivalence, all to support claims for product efficacy and safety. GCP guidelines were produced to ensure that pharmaceutical companies could not falsify data supporting product registration as the importance of not supplying ineffective products is recognised internationally. This presents a risk to animal welfare as if sick animals are treated with ineffective medicines it may be assumed that the disease is too advanced for the medication to be effective and animals will die until it is recognised that the medicine is not effective. If Australia were to support veterinary chemical registration without efficacy evaluation this represents a massive step backwards. Imagine if *Echinococcus granulosis* infection in dogs was

treated with an ineffective product, the public health implications would be huge. Suboptimal treatment of cutaneous myiasis (flystrike), *Fasciola hepatia* infection, or haemonchosis in sheep would have devastating health and welfare impacts and significantly erode the Australian reputation for animal health and welfare, undermining international trade opportunities.

The AVA supports the concept of streamlining the efficacy review and supports the concept of approval by independent, qualified, external assessment.

The AVA supports a reduced regulatory system for 'low risk' nutritional/oral products provided there is a suitable low risk framework such as the TGA 'listed' medicines system which could be set up as per Option 2. This has long been discussed with the APVMA but never established. For such chemicals the efficacy review would not be required provided the veterinary chemical included only those chemicals present on a GRAS approved list. This is similar to the END product system currently in place however this has many limitations and should be reviewed to allow for 'listed' medicines which are approved by the APVMA, manufactured to GMP standard and which meet minimum requirements. For low risk products there is always the possibility of unintended (and unforeseen) consequences and a system of monitoring the safety and effectiveness of these products should be in place that also allows changes to the regulatory status (including label changes) if adverse impacts are experienced.

There is scope for a reduced efficacy and safety assessment for products for minor use/minor species as there are very few registered products available due to the substantial costs involved in trials. Scientific argument in place of studies could be considered.

However, there are concerns among vets treating minor species (goats and camelids), particularly in respect to efficacy assessment for over-the counter products. A further consideration is that dose rates applicable to other trade species may not apply (eg goats generally require a higher dose rate of many over-the-counter anthelmintics).

Other options maybe suitable for agriculture chemicals.

6.3 Should there be greater use of standards?

Discussion questions

22) Would the ability to make greater use of standards be beneficial for applicants? If not, why?

   a) Should the use of standards be limited to products of low regulatory concern? Why/why not?

   b) Are there any unforeseen risks with adopting a standards approach like New Zealand that wouldn't require regulation changes each time a standard is created?

   c) Should the development of standards be driven by industry or the regulator?

   d) Are there any other types of standards, or approaches to self-assessment the panel should consider?

DISCUSSION

It would be beneficial for there to be a greater use of standards as this would reduce the registration timeline and encourage an increased number of products meeting a suitable standard. Use of standards should be limited to products of low regulatory concern as meeting the standard would likely allow for registration without detailed assessment of efficacy and safety which creates

unacceptable risks as outline in the answer to 6.2 above. The current New Zealand system works well and likely mutual co-operation between regulators would assist in reducing any unforeseen risks. The development of standards could be driven by either industry or the regulator to allow for more rapid development of standards. The development of a low risk registration system such as TGA listing is recommended as this would simplify the registration for many low risk chemicals. For such chemicals the efficacy review would not be required provided the veterinary chemical included only those chemicals present on a GRAS approved list. This is similar to the END product system currently in place however this has many limitations and should be reviewed to allow for 'listed' medicines which are approved by the APVMA, manufactured to GMP standard and which meet minimum requirements.

As proposed at 6.2 there could be standards or reduced efficacy and safety requirements for products for minor use/minor species, provided there was existing data available for the product in similar major species. In addition, the APVMA should allow for a reduced regulatory burden for medical devices, such as exists within the TGA.

6.4 Does Australia need to assess products that comparable regulators already agree are acceptable?

Panel's view

The Australian regulatory system needs to take full advantage of the work of comparable regulators, so that Australian effort is only focused on the issues that are unique to Australia.

Discussion questions

23) Should the regulator utilise prior assessment decisions from comparable regulators to fast track registration where appropriate? If not, why?

   a) Do you support a registration by reference approach as outlined? If not, why?

   b) Is basing the approach on decisions from one or more comparable international regulatory systems sufficient?

   c) Should the approach make it one registration for product, active constituent and label?

   d) Should the approach be used for variations and reconsiderations?

   e) Are the criteria for what constitutes a decision of a comparable regulatory system a policy decision appropriate for the minister, departmental secretary or the national regulator?

   f) What should be the requirements when considering regulatory comparability?

   g) Are there uniquely Australian issues that need to be assessed that have no international equivalence?

   h) How might the assessment of any unique Australian matters be easily managed?

DISCUSSION

Need to consider unique OHS and environmental impacts in addition to any target animal differences (eg for fish products) and any animal welfare implications that may be applicable.

The regulator should utilise prior assessment decisions from comparable regulators. Comparable regulators are well resourced with expertise in veterinary medicines regulation and it is a waste of resources and time to replicate regulatory assessment. There are certain circumstances, such as

products to treat internal or external parasites where there are local and regional issues associated with chemical resistance and lack of efficacy, local efficacy trials and assessment will still be required. However, most animal diseases occur globally and do not require specific local efficacy studies or assessment. Similarly, safety studies and safety assessments should not necessarily need to be repeated within Australia.

6.5 Does the existing approach for assessing permits (minor-use and emergency use) meet the needs of users?

Discussion questions

24) Is enough being done to address minor use permit applications, if not what more could be done?

   a) Are there any improvements or changes to the permit system that would be beneficial?

   b) Should permits be expanded beyond the activities they currently cover? If so, what activities would you suggest?

DISCUSSION

Currently it is expensive and time consuming to obtain a permit, there is little difference between a full registration and a permit. At present there are a relatively small number of registered active ingredients, particularly for minor uses and minor species. Veterinarians rely heavily on compounded medicines which are exempt from registration. If a permit system could be set up for veterinary medicines which are only available on prescription and the veterinarian is willing to take the responsibility for efficacy and safety, as they currently do for compounded medicines, a permit system with reduced regulatory requirements for efficacy, safety and even stability could be created which would ensure supply of quality manufactured products for minor use/minor species and provide an option for products manufactured by a licensed pharmaceutical manufacturing facility. There should be a pragmatic approach (in the context of risk assessment) to residue study requirements which have, historically, lead to lengthy delays in permit finalisation or withdrawal of applications for important medicines.

6.6 Should chemical reviews be timelier and more informative?

Discussion questions

25) Are there changes that need to be made to the chemical review process to accelerate timeframes for completion? If so, what would these changes be?

   a) Should reviews have flexibility to consider specific issues that warrant review rather than a comprehensive reassessment of all aspects of the original approval?

   b) Should chemical reviews be risk-based rather than driven by rolling specified timeframes?

DISCUSSION

Risk based reviews have merit.

However, a system that allowed ongoing specific reviews is needed, especially for antimicrobial products and antiparasitic products where resistance in the target organism or parasite is changing.

6.7 Should greater use of technology be used—smart labelling?

Discussion questions

26) Should smart-labels be used, what smart content should they contain and should they be machine readable?

   a) Does control of use legislation limit this approach in any way?

   b) Is mandating labels for containers above a certain volume to be machine readable supported?

   c) Should Australia adopt a comprehensive use database and/or provide access to an exact copy of the label?

   d) Should separate label approvals be removed and instead have label content specified as a condition of registration? Are current labelling requirements excessively prescriptive? Could they be made more outcomes oriented?

DISCUSSION

For veterinary prescription medicines there are advantages with flexible labelling that allows the prescriber to individualise the dose regiment for individual patients. This is an important area outside food animal practice where labelling flexibility is restrained by MRL and WHP considerations.

Inevitably as veterinary medicine use leads to greater knowledge and experience of safety and effectiveness there are refinements in use that have significant benefits in selected patients. Continuous improvement is guided by accumulated real world evidence (see introduction). Smart labelling is not the preferred way to address the evolution of product use. This should not be a regulatory matter but a matter for veterinary professional judgement based on contemporary published evidence.

Chapter 7: how can Australia build national and international capacity?

7.1 Are there sufficient international networks of expertise?

Discussion questions

27) How could the regulator and the Department of Agriculture, Water and the Environment best engage and strengthen international networks?

   a) How can parties outside of government become involved in existing international networks?

   b) How can the regulator best expand and use its existing network of international assessors?

DISCUSSION

Australia has been closely involved in the operations of VICH since its inception in 1996.

VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Its full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. VICH was officially launched in April 1996. It has 5 main objectives.

1. Establish and implement harmonized technical requirements for the registration of veterinary medicinal products in the VICH regions, which meet high quality, safety and efficacy standards and minimize the use of test animals and costs of product development.
2. Provide a basis for wider international harmonization of registration requirements.
3. Monitor and maintain existing VICH guidelines, taking particular note of the ICH work program and, where necessary, update these VICH guidelines.
4. Ensure efficient processes for maintaining and monitoring consistent interpretation of data requirements following the implementation of VICH guidelines.
5. By means of a constructive dialogue between regulatory authorities and industry provide technical guidance enabling response to significant emerging global issues and science that impact on regulatory requirements within the VICH regions.

While establishing direct relationships with the regulators of the US (CVM), Canada, Europe (CVMP) and NZ (ACVM) is important, continuing the close contact with VICH remains important and beneficial.

7.2 Is an operational regulatory working group needed?

Panel's view

The panel sees benefit in an operational group of regulators across jurisdictions focused on addressing and working through issues that need solving. This would assist in building capacity among regulators as they share information, intelligence and skills to progress their regulatory responsibilities. The panel is interested in feedback on whether there would be merit in reinvigorating the Registration Liaison Committee to focus on its original intent.

Discussion questions

28) Do you support the reinvigoration of the Registration Liaison Committee to focus on its original intent? If not, why?

    a) Do you support the proposed new formal consultative forum (chapter 5) in Australia including work on regulatory operations and technical working committees?

DISCUSSION

The Registration Liaison Committee (RLC) allowed for regular communication between the APVMA and stakeholders and reinvigoration of the RLC is supported.

If a co-regulatory model is supported for the role of veterinarians, those with substantial experience and expertise in livestock practice, including the practical challenges of managing risk of both prescription and non-prescription veterinary medicines, should be represented. Indeed, dialogue between the registering authority (APVMA) and representatives of prescribers is likely to deliver better outcomes than if regulators have a dominant role. It would also seem to be critically important that high level input from a pharmacological (particularly residue and WHP) perspective is essential.

7.3 Should the private sector be able to perform assessment work?

Discussion questions

29) Do you support a third-party accredited assessor scheme? If not, why?

    a) Do you support the scheme being based on the model in the lapsed Streamlining Regulations Bill 2019?

    b) Should applicants be able to choose their accredited assessor, or should there be a panel of assessors allocated by the regulator?

    c) Should persons overseas be able to work as accredited assessors?

DISCUSSION

Yes in principle a third-party accredited accessor scheme is supported. The regulators vet med group can only ever be very small and cannot be expected to have experience and expertise in all product categories.

There is also limited opportunity for continuing professional development of regulatory staff – an important issue that needs attention (see also 7.4 below).

The current NZ MPI uses third-party assessors and this system works very well. There are many experts in Australia who do not work at the APVMA and whose skill and expertise could be utilised in this area. Applicants should be able to choose their own assessor and persons overseas should be able to work as accredited assessors. Provided the APVMA established the requirements for approval of external assessors it should not matter who chooses the individual assessor or where they are based. For certain products, such as products to treat internal or external parasites with regional differences in resistance likely local assessment would be preferable, however overseas experts could familiarise themselves with the local data in relation to these parasites and conduct an effective assessment. This would ease the regulatory burden and be of benefit both to the APVMA and registrants.

7.4 What capabilities may be needed to adapt to future technology?

Discussion questions

30) What additional capabilities may be needed by agvet chemical regulators to assess new technology?

   a) Which stakeholders should agvet chemicals regulators consult with to stay abreast of current and emerging technologies?

   b) What horizon scanning activities should be undertaken by agvet chemicals regulators?

DISCUSSION

Two avenues should be considered:

1. A standing veterinary medicines consultation between the veterinary profession and the regulator will enable the veterinary medicines regulator to remain in close contact with current developments and future needs of the veterinary profession. Amongst the 10,000 practicing veterinarians there is a huge repository of knowledge and experience that is available for mining in the consultation process.

2. The necessarily small contingent of veterinary medicine regulatory professionals need to have their training needs assessed and a training programme developed. While local university training could be developed to meet induction requirements, secondment to or time spent participating in training programmes undertaken by larger regulatory agencies (for example CVMP or CVM) is likely to be beneficial.

The process of professional development is just as important for regulatory veterinarians and non-veterinarians as it is for practicing veterinarians. The application of the new knowledge gained needs to be overviewed within the organisational structure to ensure that local regulatory approaches are retained and overseas approaches, while considered, are not automatically adopted.

Chapter 8: how will a new regulatory system be sustainably funded?

8.1 Are all system users paying their fair share of costs?

8.2 Are fairer cost recovery arrangements needed?

Discussion questions

31) Which proposed cost recovery options presented do you support and why?

   a) Which combinations of the proposed options work best together and why?

   b) Are there other options that the panel should consider?

DISCUSSION

Cost recovery – the current system encourages the provision of products with low sales volumes and helps fill the therapeutic gaps that would not be filled if full fee-for service was introduced. With full fee-for service we are likely to see big pharma with blockbuster products continue to prosper and the needs of producers for specific low use products unmet. However the current ability for copy products to be registered at a fraction of the cost of those who provide the research is also highly inequitable and greatly reduces the incentive to develop new products except in those jurisdictions where registration within the life of a patent is possible. However not all new product developments will be patentable.

8.3 Are there 'public goods' government should fund?

Discussion questions

32) Which regulatory activities outlined do you think represent a public good and why?

   a) Are there other activities not mentioned that could represent a public good? If so, what are they?

DISCUSSION

Some compliance would definitely be a public good and if government funded would help remove the complaint that the regulator is funded by the regulated and therefore beholden to it. Environmental monitoring is an area that could be considered a public good in some instances.

It is suggested that public good is measurable by market access/trade and by animal welfare expectations of the community.

Public good also extends to include OH&S aspects for users of veterinary medicines and the availability of safe food free from pathogens and unacceptable chemical residues

Chapter 9: Appendix A: independent review: agvet chemicals national regulatory framework

Other issues for consideration

NEED FOR FLEXIBLE LABELS

There is a special case for veterinary medicines where the target of drug action changes with product use and the dosage regimen therefore needs periodic adjustment: the case of antimicrobial resistance and antiparasitic resistance (blowflies, ticks, lice, coccidia, nematodes, trematodes).

WITHHOLDING PERIOD CHANGES AND NEED FOR COLLABORATIVE APPROACH

Impact of changing dose rates on withholding period determination. A system is needed that allows data collection on residue concentrations in food producing animals treated off-label. Such data could lead to evidence-based recommendations on future uses.

VETERINARY MEDICINES FOR SMALL ANIMALS, HORSES, FAUNA, ZOO ANIMALS AND EXOTIC SPECIES

There is a significant difference between agricultural chemicals and veterinary medicines. The health and welfare and quality of life of animals is an important consideration every time a veterinary medicine is used. Veterinarians deal with sentient animals. Agricultural products are applied to crops and plants and other non-animal non-sentient species. Regulation of veterinary medicines is much more closely aligned to the regulation of human medicines. There are very few major regulatory agencies that have responsibility for regulating both ag and veterinary products. IN the US, the FDA reviews human and animal products. In Europe, the EMA reviews human and animal products. Similarly, in Canada and many other countries. The US EPA regulates external non-systemic pesticides used in animals and all pesticides used in plants – however, this co-registration is a very small part of the veterinary medicine world. Before the APVMA and the NRA, the regulatory system in Australia regulated veterinary medicines separately (via the Technical Committee in Veterinary Drugs or TCVD). The question: why mix ag and vet chemicals?

ESSENTIAL NEED FOR VETERINARY MEDICINES THAT ARE UNLIKELY EVER TO BE REGISTERED

Registration will only ever apply to a small number of the veterinary medicines used by veterinarians. The regulatory system needs to recognise this and the role of veterinarians in using medicines that are essential but not registered.

DIAGNOSTIC TESTS

Appropriate and effective selection and use of veterinary medicines relies on an accurate diagnosis. Veterinarians utilize the history of the circumstances, physical examination and a variety of tests to develop a provisional or definitive diagnosis. A variety of diagnostic tests are marketed in Australia and sold to veterinarians. Not all tests are subjected to validation, for example to determine sensitivity and specificity. Some tests have been found to be unreliable and inaccurate. If animal health and welfare is dependent on appropriate treatment and if treatment in turn is dependent on the diagnosis which itself is dependent on a test that claims to provide diagnostic information, then the accuracy of the test and validation of the testing method is essential. This is an area that does not seem to be regulated other than by consumer law. However, protections of consumer law arise only if diagnostic tests are shown to be inaccurate which can only happen after inaccuracy is discovered, which may only occur if a large number of animals experience treatment failure.