Draft Report of the Independent Review of the Agvet Chemicals Regulatory System

Submission from the Australian Veterinary Association Ltd

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The Australian Veterinary Association (AVA)

The Australian Veterinary Association (AVA) is the national organisation representing veterinarians in Australia. The AVA consists of close to 9000 members who 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 Association.

Summary of documentation supplied

AVA is pleased to offer the following feedback in response to the ***Draft Report of the Independent Review of the Agvet Chemicals Regulatory System (the Draft Report).***

Please note that our feedback consists of:

1. An introductory discussion paper (follows)
2. A copy of the Draft Report, throughout which we have inserted comments and suggested tracked changes that we believe warrant inclusion in the final report (**ATTACHMENT A**).
3. A document setting out the Draft Report's Recommendations, along with AVA's comments and suggested tracked changes (**ATTACHMENT B**)
4. AVA's Decision Flowchart for use of compounded products by veterinarians which we believe should be adopted in preference to "List A" in Annex 9 of the Draft Report (**ATTACHMENT C**)

Veterinary Medicines: Key Points

1. **Quality assurance** of veterinary medicine products is essential
2. **Efficacy (and effectiveness and safety)** is an essential requirement for registered veterinary medicine products
3. Registration of all veterinary medicines for production animal species is 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 regulatory support is required to enable veterinarians to establish an appropriate WHP
4. Veterinary practitioners require **access to suitable veterinary medicines for all (>1,000) species** they care for. This will necessitate the complementary sources of registered and compounded products, both within the remit of the APVMA.
5. For unregistered products systems for collecting **real-world data (RWD) and real-world evidence (RWE)** to support dose regimens, effectiveness, and safety is desirable
6. **Postgraduate training, continuing professional development and annual registration** 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.
7. Within the **One Health** area, veterinarians work closely with other professionals to protect animal, human and environmental health.
8. 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, the availability of which should be facilitated by the regulatory system.
9. A regulatory system that facilitates and supports the availability of veterinary medicines and **works closely with the veterinary profession** is the most desirable outcome.
10. 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.
11. The most refined and responsive system of veterinary medicine availability and individualisation requires **ongoing monitoring of use with appropriate and timely feedback** to veterinary prescribers to allow targeted modifications.
12. A regulatory system would benefit from an effective connection between the regulatory system and the **social license** of producer industries. Veterinarians are increasingly involved as advisors to or in senior roles within many producer industries, having responsibilities for animal health and welfare and therefore could play an influential role in connecting the regulatory system to current and future use of veterinary medicines.
13. **Diagnostic tests** can often underpin accurate diagnosis and the development of treatment plans. Such tests should be accurate and reliable and validated to ensure they provide appropriate information. There is currently no requirement to validate diagnostic tests.
14. The use of veterinary medicines especially (but not exclusively) those in Schedules 4 and 8 of the SUSMP (Standard for the Uniform Scheduling of Medicines and Poisons) in the diversity of species presenting to veterinary practitioners, can require specialised experience and expertise. It is recommended that The Commissioner form a **Standing Advisory Panel on Veterinary Medicines** to take advantage of the vast repository of skills present within the veterinary profession. This will increase the likelihood of avoiding any unintended consequences of policy and other decisions.

Introduction

Veterinary practitioners are well qualified professionals whose practice of veterinary medicine at a standard that meets the expectations of their clients increasingly requires access to a vast number of veterinary medicines of suitable quality, safety, and effectiveness and with a suitable dosage form – if the product cannot be administered then it cannot be effective. The veterinary profession relies on the veterinary medicine regulatory system to facilitate access to needed medicines of appropriate quality. The Australian veterinary profession is regarded highly by its global counterparts. In a country with a significant livestock population and with growing importance of companion animal species, veterinarians fulfill an essential role in caring for animal health and welfare.

The Current Situation

Training and Qualification of Veterinarians

Australian veterinarians of today and the future complete a postgraduate doctoral degree to gain the degree of Doctor of Veterinary Medicine (DVM). The postgraduate study provides veterinarians with the competencies to participate in a profession that can attend to the health and welfare of all non-human animal species. The comprehensive training in biology, chemistry, anatomy, physiology, pharmacology, microbiology, parasitology and the multiple constituents of veterinary medicine and veterinary surgery. Knowledge and experience of these subjects provide a solid foundation for the diagnosis of physiological abnormalities and of disease and development of a therapeutic plan that includes the selection and use of the most appropriate veterinary medicines.

Veterinary Professionalism

Professionalism has been defined as "...a combination of knowledge, skills, trustworthiness and altruism found in those who commit themselves to a life of service to others" (Beaton 2010).

Vandeweerd et al (2012) emphasised that the veterinary profession "has the ethical obligation to provide effective and safe treatments and recommendations in a rapidly changing market with both more price-conscious clients and a more demanding regulatory environment. Careful decisions are required to minimise potential liability risks."

In a commentary on the future of the professions, Susskind and Susskind (2015) summarised society's view of professions by noting that "in acknowledgement of and in return for their expertise, experience and judgement, which they are expected to apply in delivering affordable, accessible, up-to-date, reassuring and reliable services, and on the understanding that they will curate and update their knowledge, and methods, train their members, set and enforce standards for the quality of their work, and that they will only admit appropriately qualified individuals into their ranks, and that they will always act honestly, in good faith, putting the interests of clients ahead of their own, we (society) place our trust in the professions in granting them exclusivity over a wide range of socially significant services and activities, by paying them a fair wage, by conferring upon them independence, autonomy, rights of self-determination and by according them respect and status".

Clearly veterinarians, as professionals, have demanding responsibilities which when performed with skill and aptitude can earn the trust of society. It is maintaining this trust that provides the veterinary profession with a social licence to continue their work. Trust can be undermined and lost readily, and veterinarians understand that every action is scrutinised and must be undertaken to the highest standards.

The clients of veterinarians, and society as a whole, expect veterinarians to select and use the most appropriate veterinary medicines available. Veterinarians in turn rely on the expertise of the regulator of veterinary medicines to assess new medicines thoroughly before registration. Veterinarians rely on the

label of registered products to provide essential information on the indications for the medicine, the dosage regimen and the precautions that must be observed. This is a fundamental role of the regulator, as products that do not perform as expected, especially those that are ineffective for the label indication, can seriously and irreversibly effect the health and welfare of treated animals.

Animals under the care of the veterinary profession

The veterinary profession is becoming increasingly focused on the needs of its clientele. For both production (food and fibre production) animal and non-production animal species 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 the use of veterinary medicines.

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 animal 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 (MRLs) 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 otological 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 new manifestations of disease due to prokaryotic (bacterial and viral) and eukaryotic (protozoal and fungal) 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 the 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.

Unmet therapeutic needs

The therapeutic needs of the vast number of exotic animal species can be appreciated by a glance at the exotic animal formulary edited by Carpenter and Marion (2018). The formulary includes sections on invertebrates (including abalone, bees, cephalopods, clams, conches, coral, cuttlefish, lobsters, oysters, polychaetes, sea urchins, shrimp, spiders, starfish), fish, amphibians, reptiles, birds (thousands of species), sugar gliders, hedgehogs, rodents, rabbits, ferrets, miniature pigs, primates, waterfowl and wildlife (thousands of species). The formulary provides information on 678 pharmaceutical active constituents plus 80 combinations of these actives. Most of the medicines are included in the categories of analgesics, anaesthetics (inhalant and injectible), antiepileptics, antifungals, antibacterials, antiparasitics, antiprotozoals, antivirals, chemical restraint agents, chemotherapy, and euthanasia agents. Very few (less than 5%) of the products described in this publication (now in its 5th edition) have suitable registered products available.

While Carpenter and Marion (2018) provide a global picture, closer to home and in Australia, a search of the APVMA product database (PubCris) reveals no veterinary medicines registered specifically for emus, 3 products for each of kangaroos and wombats (3 different ketamine injectible products) and 4 products for the koala (3 ketamine injectibles and paralysis tick antivenene). Products registered with broad claim for ANIMALS, which would include Australian fauna species, total 32 products, principally classified as euthanasia injections, tetracycline topical powder and aerosol, enrofloxacin oral and injectable products, antiseptics, disinfectants, wound treatments, probiotics, and parenteral fluids. Clearly the therapeutic formulary or registered veterinary medicines to meet the many clinical needs of Australian fauna is extremely deficient.

Registration to meet unmet needs

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 adverse impacts 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 is 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 they 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 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 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 a WHP. However, capturing information on the effectiveness and safety of this ELU will also have significant benefits in refining the treatment of new species. For example, sarcoptic mange in free-ranging bare-nosed wombats (*Vombatus ursinus*) is a significant source of morbidity and mortality. Collection of RWE of the response to treatment of wombats with various forms of moxidectin revealed evidence of safe and effective use, establishing the foundation of a hypothesis to be tested in future controlled studies (Old et al 2021). If substantiated to be effective this treatment approach could save the lives of many wombats. Studies such as this one provide the foundation for safe and effective ELU.

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 in the 4 week response time permitted. 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 expected 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 and welcomes the recommendations of the AgVet Review panel.

Emerging Trends in Veterinary Medicine

Megatrends

Key issues driving change in the Australian livestock industries include increased focus on food safety, product integrity and health benefits, corporate social responsibility, production systems and innovations, sustainability, and traceability (Begley et al 2019). The megatrends that need to be addressed include climate change megatrends that are re-shaping terrestrial and aquatic animal production systems; consumer megatrends that are creating increased global demand for meat as well as alternative, more sustainable choices for protein and fibre; technology megatrends that offer extensive opportunities to support the sustained prosperity of livestock industries; changes in Government resourcing and shifts to user-pay systems that exacerbate the need to achieve improvements in resource use efficiency; and the move to intensive and free-range production systems that could, if managed poorly, increase the pressure on antibiotic usage (accelerating anti-microbial resistance) and increase the risk of (animal and zoonotic) disease.

In the face of these trends, there is an aspiration for Australian agriculture to be a $100 billion industry by 2030 (NFF 2019).

Veterinarians are well positioned to address the megatrends and assist industries meet their aspirations for growth. However, a facilitating veterinary medicines regulator is a key element of a successful future.

Precision veterinary medicine

Precision veterinary medicine is a key element in meeting the challenges of the future. 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. Already new technologies are allowing substantial improvements in disease detection and diagnosis (Mayer 2021; Neethirajan 2017; Sharma 2021), dose precision (Darwich et al 2021; Martin and Olver 2021), drug formulation (Bhansali et al 2021; Dabholkar et al 2021) and delivery (Rahimi et al 2021; Salahpour-Anarjan et al 2021).

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). In some cases, special study designs can optimise the selection of treatments for individuals (Davidson et al 2021)

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. 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). The FDA has recently release an app to help data collection (Wyner et al 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.

New veterinary medicines

It is not expected that new antibacterial agents will become available for use in production species due to the crisis in global public health associated with increasing resistance and absence of truly novel antibacterial agents – anything new is likely to be used only for human use. New technologies in are likely to assist the health and welfare of production and non-production animals (Klerkx and Rose 2020; Varela et al 2021), including regenerative medicine (Godbey 2022a), transgenics (Godbey 2022b). New veterinary product types for non production species include gerobiotics (Tsai et al 2021), psychobiotics (Sharma et al 2021) and senolytics (Robbins et al 2021). Opportunities for repurposing of existing medicines may be disclosed by analysis of electronic health records (Ozery-Flato et al 2020).

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).

The drivers of antibacterial resistance are becoming clearer (Booton et al 2021) as is the likelihood of emergence of new infectious bacterial and viral diseases (Dash et al 2021; Fisher and Murray 2021). Awareness of zoonotic diseases by veterinary and medical practitioners is in need of improvement (Steele et al 2021).

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.

Many alternatives to antibacterials are being reported (Atterbury and Tyson 2021; Davar et al 2021; Kumar et al 2021; Mishra et al 2021; Premaratne et al 2021) and the role of vaccines in attenuating the importance of AMR is increasing (Jansen et al 2021; Micoli et al 2021).

The veterinary profession has an another important mission to play in the One Health Master Plan for Australia's National Antimicrobial Resistance Strategy – 2020 and beyond (Department of Health and Department of Agriculture, Water and the Environment 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 facilitates 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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