Veterinary Medicines Directorate

VMD Regulatory Science Strategy

November 2020

Version: Consultation 18 November 2020

1.Introduction

1.1 Overview

The Veterinary Medicines Directorate (VMD) protects animal health, public health and the environment and promotes animal welfare by assuring the quality, safety and efficacy of veterinary medicines.

The VMD's strong scientific expertise is recognised in its robust assessment of national marketing applications and previously in the lead role that the agency has taken in the assessment of marketing applications at the European level and the significant contributions the agency's staff have made to the scientific guidelines prepared by the European Medicines Agency's scientific working parties. More recently, the VMD has become more global in focus, building partnerships for joint international scientific assessments of marketing authorisations and developing medicines regulation capability in less developed countries.

The rapid developments in science and technology in recent years have resulted in innovative medicines and novel scientific models and tools. It is essential that the UK regulatory framework enables the assessment and acceptance of new and innovative technologies and that these assessments are based on scientific, evidence-based decisions.

There is also an increasing awareness of the impact of medicines on the environment and the public health consequences of antimicrobial resistance. In parallel, there is a growing demand for products that fall on the borderline between veterinary medicines, biocides and feed additives, which are administered with a view to, not only support a reduction in antimicrobial use, but also control emerging diseases and maintain efficiency of livestock production. The continued drive to improve animal welfare in testing through 3Rs methodologies is gradually leading to replacement of some animal studies with *in vitro* and *in silico* tests. Throughout the product life cycle, the approach to pharmacovigilance is changing to take advantage of modern methods to improve data collection and analysis. The VMD must be ready to embrace these challenges and form collaborative partnerships with stakeholders to ensure development in these areas.

The purpose of this regulatory science strategy is to ensure that the VMD keeps abreast of, and anticipates future, technological advances and novel approaches, in order that we are well equipped to address the scientific and regulatory challenges that will arise over the next 10 years.

1.2 Vision and Objectives

The vision and objectives of the regulatory science strategy are as follows:

Vision

To promote the scientific basis underlying the authorisation and regulation of veterinary medicines, ensuring the availability of products which support animal health whilst protecting public health and the environment.

Objectives

- To ensure that the VMD maintains a modern regulatory framework for veterinary medicines, underpinned by good science.
- To support a flexible regulatory environment to enable the VMD to respond rapidly in emergency situations, with a proportionate approach to managing risks.
- To ensure that assessment approaches can be adapted to take advantage of scientific developments.
- To ensure that the VMD's scientists have the knowledge and skills to deal with current and future challenges and innovations.
- To encourage knowledge exchange with other regulatory bodies (national and international), research communities, pharma partners, Defra and other government departments.
- To develop a network of external specialists to provide advice and training.
- To identify research needs.

1.3 Consultation

The purpose of this consultation is to share the VMD's proposals with our stakeholders and to gain feedback on whether stakeholders agree with our priorities, and/or have suggestions for other areas where we should focus our efforts.

Please provide any feedback or comments to g.clarke@vmd.gov.uk by **31 January 2021.**

2. Strategic Goals

The VMD has identified six strategic goals for this regulatory science strategy:

1. Enabling access to novel therapies and technologies
2. Addressing emerging health threats
3. Enabling availability of veterinary medicines
4. Strengthening a life cycle approach to benefit-risk assessment
5. Facilitating the use of novel scientific models and tools
6. Ensuring access to high quality regulatory scientific expertise

2.1 Enabling Access to Novel Therapies and Technologies

Rapid advances in biotechnology are bringing forward innovative medicines which will broaden the range of preventative medicines and treatments available for a variety of diseases. The development of novel therapies is an attractive prospect for industry. For example, the first veterinary monoclonal antibody product was authorised in the UK in 2017 for the treatment of atopic dermatitis in dogs. In the same year, the first DNA plasmid vaccine was authorised, offering protection to salmon against pancreas disease and in 2019 two allogeneic stem cell products were approved for the treatment of lameness in horses.

Future areas of relevance to veterinary medicine may include novel therapies based on bacteriophage, novel delivery systems such as nanotechnologies, RNA vaccines, CRISPR gene editing and gene therapy.

However, novel therapy veterinary medicines can present challenges for the classical regulatory paradigms and the lack of a specific regulatory framework for these products has been problematic. There are an increasing number of complex enquiries from academia and industry concerning the development of novel therapies and/or their regulation, so it is critical that the VMD continues to develop and expand its expertise in this area and, where we identify that in-house expertise be augmented, establishes a network of independent advisors.

2.1.1 Support the development of novel therapies

Novel therapy veterinary medicinal products (NT-VMPs) are a group of products that often do not fit into the classical division of veterinary medicines as immunological and non-immunological veterinary medicines. This demands that a more tailored regulatory approach is established for these products, acknowledging the unique challenges presented by each sub-category of NT-VMPs.

Over recent years, there has been a significant increase in the number of veterinary medicines under development that fall into the classification of NT-VMP and, based on horizon scanning, this trend appears set to continue. To some extent, this mirrors the research and development of new medicinal products for use in human medicine, many of which have provided hope in areas of previously unmet clinical need. Therefore, regulatory authorities globally, and in both the human and veterinary sectors, are keen to support the development and availability of novel therapies. Indeed, there is significant opportunity for collaboration and for both human and veterinary sectors to learn from one another’s experiences.

In order to be best prepared to evaluate the quality, safety and efficacy of novel therapies and to conduct appropriate benefit-risk assessments throughout the product life cycle, it will be important that the VMD continues to expand its access to the necessary expertise to conduct scientific assessments and support decision making. It is important that skills gaps are identified at an early stage and the required expertise developed through training, or otherwise accessed through external recruitment or networking.

Furthermore, to facilitate the development of NT-VMPs and promote innovation, the VMD must ensure that there is a clear regulatory path to market. This will include development and continual review of a regulatory framework for emerging novel

therapies that is fit for purpose, and development of high-quality scientific guidance that support companies in better understanding these regulatory requirements.

To support the development of novel therapies, the VMD will look to:

- coordinate horizon scanning activities in relation to NT-VMPs, i.e.:
    - review horizon scanning signals and prioritise those areas where the most significant activity is taking place.
    - identify areas where scientific guideline development is most urgent to support development of NT-VMPs, based on horizon scanning and stakeholder engagement.

  This will be taken forward though the VMD's Novel Therapies Group, the remit of which is to discuss products under development and to horizon scan for early identification of regulatory challenges and risks.
- review the need for reform of the regulatory framework for NT-VMPs in order to facilitate the development and authorisation of novel therapies and technologies for use on the UK market.
- increase the availability of scientific and regulatory guidance that facilitates the development and marketing of novel therapies and technologies in the UK, thereby increasing access to such products in the UK.
- review and optimise the VMD's support structures to ensure companies continue to be able to access scientific and regulatory advice services for NT-VMPs.
- develop and maintain a database reflecting the VMD's own expertise in key areas and establish and maintain a network of independent advisors prepared to support the VMD with its future work.

2.1.2 Facilitate the development of allergen immunotherapies

Allergic diseases are growing in importance in veterinary practice[1]. Allergen immunotherapy extends treatment options available for companion animals, typically those suffering with chronic atopic skin disease. However, applications for marketing authorisations present scientific and regulatory challenges. Firstly, allergen products may be derived from diverse natural sources and contain a mixture of extracts, leading to specific requirements for their quality control. In addition, patients are treated as individuals, and specific immunotherapy (SIT) is reliant on accurate diagnosis of the allergens of relevance to the patient. Clinical field studies in sensitised animals are considered to be the most appropriate means to demonstrate the safety and efficacy of SIT[2]; however, the complexity of the treatment for individual animals may present difficulties for study design and interpretation. Additionally, recent advancement in human medicine is the use of recombinant DNA

[1] Marsella, R. & De Benedetto. A. (2017) Atopic dermatitis in animals and people: an update and comparative review. *Vet Sci*.4 (3). p.37

[2] European Medicines Agency (2018) *Draft* guideline on requirements for the quality, safety and efficacy of allergen products for use in horses, dogs and cats. EMA/CVMP/IWP/170689/2016

technology to produce pre-defined allergenic proteins and it is expected that this could also be introduced for diagnosis and SIT in veterinary patients.

There are currently no allergen immunotherapy products authorised in the UK. This is an area of unmet clinical need and under the VMD special import scheme, allergen products are consistently in the top 10 of imported products. Although there is a European Pharmacopoeia monograph on Allergen Products (1063), five monographs on source materials, and an EU guideline[3], this collective guidance requires updating to provide clarity on quality, safety and efficacy aspects of allergen products and to reflect scientific advancements, including consideration of allergens manufactured using recombinant DNA technology.

To facilitate the development of allergen immunotherapies, the VMD will look to:

- develop a fit-for-purpose UK regulatory framework to facilitate submission of applications for allergen products, thus assuring the quality, safety and efficacy of allergen immunotherapies.
- elaborate guidance on the requirements for allergenic immunotherapies, including specific guidance for the use of recombinant DNA technology in allergen immunotherapy.
- support the development of novel products: exploring the advancement of knowledge/research in the human field on the use of allergens manufactured using recombinant DNA technology and potential application to veterinary medicine.
- based on horizon scanning, strengthen support to industry throughout the development life cycle and facilitate the development of novel allergen immunotherapies, including advancement of knowledge/research in the human field to veterinary medicine.

2.2 Addressing Emerging Health Threats

Climate change and increasing international movement of animals and animal produce have heightened the threat of disease incursions into the UK, as evidenced by the outbreaks of Schmallenberg and Bluetongue virus infections in recent years. The emergence and development of such disease outbreaks may be rapid and so the VMD needs to be proactive and ready to respond as and when necessary. It is essential, therefore, to ensure we maintain an awareness of emerging diseases at an early stage, expertly consider the potential impact of global diseases on the veterinary industry in the UK in partnership with other experts in the area, and react in a timely manner to provide clear guidance and appropriate support to a range of stakeholders.

[3] European Medicines Agency (1994) Specific Requirements for the Production and Control of Allergen Products (7BIm11a)

2.2.1 Facilitate access to medicines to prevent, treat and control emerging diseases

The UK Veterinary Medicines Regulations (VMR) allows expedited response to emerging disease situations under an 'exceptional circumstances' provision, which permits applications to be submitted without the complete quality, safety or efficacy documentation. Currently, the UK can issue a provisional marketing authorisation (PMA) to help address an urgent situation related to an emerging disease. This route to authorisation allows for a reduction in the data requirements that can be accepted to conclude a positive benefit-risk balance for a product. The data package would then be completed using data from use of the product in the field situation. It is essential that the VMD is ready to provide accurate guidance in an expedited manner to manufacturers detailing the minimum data requirements.

This will ensure that there is:

- increased, and more rapid, progress to market for medicines to prevent, treat and control emerging diseases via:
  - building on existing networks to maintain an early awareness of new diseases that might impact the UK and in which veterinary species are involved.
  - the ability to objectively rate the risks of such diseases via an understanding of the potential impact of the disease in the UK and the required timeframe for the response.
  - improved guidance for industry on how the data requirements for a PMA might be reduced, depending on the risk rating for the given emerging disease and proposed veterinary medicine.
- improved engagement with stakeholder groups and creation of networks to facilitate collaborative action in the event of emergence of a significant new disease.

To facilitate access to medicines to prevent, treat and control emerging diseases, the VMD will look to:

- critically review how emerging diseases have been dealt with historically, including the effectiveness of previous PMA applications.
- review existing legislation to identify areas where translation, omission or augmentation of the existing legislation may be required.
- review current guidance on the 'exceptional circumstances' provision and consider how this can be clarified, expanded or otherwise improved.
- enhance the existing systems for monitoring for the emergence of new diseases.
- establish a risk rating system for new diseases which will be linked to guidance on reduced data requirements.
- consult with stakeholders about the potential difficulties faced when developing veterinary medicines to prevent, treat and control emerging diseases and how these might be overcome.

- identify research gaps relating to the development of new diagnostics, vaccines and pharmaceuticals to improve the control of infectious animal diseases.

2.3 Enabling Availability of Veterinary Medicines

An appropriate range of medicines to prevent and treat diseases in animals is critical to ensure animal health and welfare and protect human health. However, availability of medicines in some areas could be significantly improved.

The VMD has a number of initiatives to improve availability, including the prescribing cascade, which includes the special import scheme and the exceptional MA schemes – a limited MA (LMA) to help fill an existing therapeutic gap and where the product is not expected to be sold in vast quantities, and a provisional MA (PMA) to help address an urgent situation, both of which may be granted on the basis of a reduced data package. Nevertheless, there may be opportunities to review the regulatory framework to see whether progression to market of additional and/or alternative veterinary medicinal products can be encouraged.

2.3.1 Encourage the development of borderline therapeutics

The VMD is often required to provide advice on whether particular healthcare products for use in animals fall within the regulatory framework for veterinary medicines. Alternatively, such a product might fall within the remit of the Health and Safety Executive (HSE), if classified as a biocide, or the Food Standards Agency (FSA), if determined to be a feed additive. However, certain veterinary healthcare products fall outside both the strict definition of a veterinary medicine and classification as a biocide or feed additive. As a consequence, these products may be marketed in the UK without regulation.

The VMD will reflect on the need for regulation of products that fall outside the confines of the definition of a veterinary medicinal product. Although these products may not fulfil the usual requirements for a marketing authorisation, e.g. demonstration of a particular efficacy threshold; they could have other benefits, such as improved safety compared with conventional medicines, or function as alternatives to traditional antimicrobials or anthelmintics, Other products may not have any obvious benefit to the animal, but may have a positive impact on the environment. This would include administration of chemical inhibitors to cattle to suppress methane production and help meet targets of reducing greenhouse gas emissions.

The VMD will consider how these products might be regulated from a legal and scientific perspective and review our data and regulatory requirements with the aim of improving availability while also ensuring their quality, safety and efficacy. This would provide end-users with better guidance as to the expected benefits and potential risks resulting from product use. The VMD will ensure that a consistent approach is taken between similar products, seeking input from colleagues at HSE, FSA and other regulatory agencies as identified.

To encourage the development of borderline and neglected therapeutics, the VMD will look to:

- conduct a review of those UK products, currently considered to be borderline veterinary products, to determine the types of product the VMD's regulatory strategy should focus on, the typical claims made for these products, and the regulatory approach historically taken.
- review advice given by VMD, HSE and FSA and consider whether further collaboration is required.
- review how veterinary and human borderline products are regulated in other jurisdictions, including permissible claims, and consider whether joint regulation with other veterinary medicine agencies might be appropriate to improve availability of borderline medicines.

Having explored the above, the VMD will look to:

- undertake appropriate research and/or scientific training and consult with experts in the field to gain a greater understanding of the risks versus benefits of these products.
- identify a list of product types which might benefit from a new regulatory framework.
- propose and consult on options for potential regulatory framework(s) for each product type and required standards for borderline products, considering the benefit-risk analysis of each.

2.3.2. Promote alternatives to antimicrobials

The AMR threat is a high priority for government and the UK's five-year national action plan[4] highlights plans to work with industry to deliver a sustainable supply of high-quality, new and alternative preventative medicines and treatments, and to reduce animals' exposure and susceptibility to pathogens which will, in turn, reduce the need for antimicrobial treatment.

Alternatives encompass a wide range of therapeutics that could reduce antimicrobial consumption, by either preventing, treating or reducing the risk of bacterial infection. Some products also bring additional health benefits, such as increased resilience to disease. Examples include novel therapies based on bacteriophage, phytochemicals, antimicrobial peptides and immunomodulators. These substances often fall under the area of 'borderline products' and are accompanied by the regulatory challenges identified above (see section 2.3.1). An improved understanding of the mechanism of action of specific types of product could help direct their development pathway.

It is important that the VMD has a clear and consistent regulatory position, providing scientific and regulatory advice in appropriate areas, and guiding legislative decision making.

[4] HM Government. (2019) Tackling antimicrobial resistance 2019–2024.

To promote alternatives to antimicrobials, the VMD will look to:

- define the key regulatory terms (*alternatives to antimicrobials* and *novel antimicrobials*) and consider the need for additional terms to define other important product categories, e.g. categories of active substance that target antimicrobial resistance mechanisms.
- issue guidance to ensure applicants understand that they may be eligible for a limited marketing authorisation, where the market is anticipated to be small, e.g. for some vaccines intended to be used as alternatives to antimicrobials.
- identify regulatory strategies that will increase the development, availability, and use of alternatives to antimicrobials.
- establish a clear picture of the pathway(s) to market for the major classes of product currently falling under the classification 'alternatives to antimicrobials'.
- where necessary, provide additional clarification of the data requirements and claims that may be appropriate.
- improve clarity regarding the borderlines between the UK VMR, Biocidal Product Regulations, and Feed Additives Regulations to provide clarity as to which regulations a product will fall under. This work will focus on animal health products that target bacteria.

2.4 Strengthening a Life Cycle Approach to Benefit-Risk Assessment

Benefit-risk assessment is a tool to support the regulator’s decision making and should be a consistent and transparent process that is performed throughout the life cycle of the medicine.

However, the validity of the benefit-risk assessment is dependent on the quality and quantity of the data available and may rely on an appropriate interpolation technique if data sets are limited, or interpretation of large diverse and conflicting data sets.

When risks are identified, suitable risk mitigation measures need to be put in place, which may range from safety warnings on the packaging, to post-marketing risk management plans. In all cases, communication of risk needs to be tailored to the appropriate audience using suitable language and taking account of differing levels of knowledge.

A review of the benefit-risk methodology is essential to ensure that the approach is fit for purpose and to identify whether improvements can be made, either through new approaches or refinement of existing ones.

2.4.1 Improve the consistency and transparency of benefit-risk assessment

Benefit-risk assessments for veterinary medicines are usually performed on the basis of a qualitative approach that relies on expert judgement. Adopting a more quantitative approach is not straightforward, owing to the diversity and complexity of factors, including risks to the target animal, user, consumer and the environment. However, the use of a more structured and/or a quantitative framework would

improve the consistency and transparency of decision-making, with clearer description of treatment benefits and risks/harms in terms of effect sizes and the (un)certainty around their estimation.

Improved regulatory transparency has the potential to benefit the end user by facilitating a more meaningful comparison of products to inform treatment selection. An investigation into different approaches would need to give specific consideration to the benefit-risk assessment for marketing authorisations granted under the exceptional MA schemes – limited MA (LMA) or provisional MA (PMA), where there may be a relaxation of usual data requirements. Guidance on how these potential reduced data packages may affect the benefit-risk assessment is currently sparse.

Currently, assessment of product benefits focusses on the benefits to the target animal(s), with only minor consideration to additional benefits, particularly those not involving the treated animal. Other benefits, such as positive impacts regarding public health or the environment could be considered, thus promoting a more holistic assessment of the benefit-risk balance.

Similarly, the benefits and risks of a new product are not compared with those of similar, already authorised products or treatment modalities. Owing to the varied risks and benefits of veterinary medicines to the target animal, but also risks to the user, consumer and environment, there may be merit in such comparisons. Also, consideration could be given to the relative impact of the veterinary product compared to the use of the active substance(s) in other industries (e.g. when determining risks to the environment).

Advancements in data modelling may result in a reduction in the industry's reliance on traditional *in vivo* animal studies. It is essential that the benefit-risk framework can accommodate these changes. For example, new types of data and approaches to their analysis may impact on the precision and uncertainty around estimates, or the representativeness of the data to the target population. The impact on the benefit-risk assessment of the use of surrogate or proxy clinical endpoints and novel biomarkers needs to be considered.

To improve the consistency and transparency of benefit-risk assessments, the VMD will look to:

- investigate the suitability of alternative benefit-risk methods, including quantitative/semi-quantitative approaches and targeted approaches.
- investigate whether a broader range of benefits may be incorporated into the benefit-risk assessment and whether comparison of benefits and risks between products/treatment modalities could be beneficial.
- collaborate with experts to ensure that any new methods are adaptable to advancements in data modelling and subsequent reductions in number/size of traditional *in vivo* animal studies.
- 'test' the quality/added value of potential new benefit-risk models through, for example, selected re-assessment of completed applications followed by pilot testing alongside the current approach.
- investigate potential for improvement of communication of risks and risk mitigation strategies.

- ensure appropriate training of assessors.
- consult and provide guidance to industry on the new approach to benefit-risk assessment.
- consider appropriate methodologies for ‘exceptional circumstance’ and limited market applications, given the reduced data requirements.

2.4.2 Improve signal management in analysis of pharmacovigilance data

Public concerns about the safety of veterinary medicines continues unabated. There is also an increasing need for availability of a wide range of medicines providing tailored individual treatment in an era of preventative medicine with reduction of zoonoses and antimicrobial use. The evaluation of safety signals is essential to provide regulatory authorities with up-to-date information on a medicine's benefits and risks, to assess if the benefit-risk is still favourable.

Signal management is a set of activities aimed at detecting, prioritising, validating and evaluating the risks associated with use of a veterinary medicine (or active substance) in the field following its authorisation[5]. Where necessary, regulatory action can then be implemented to minimise identified risks. Signal data are obtained from surveillance of adverse event (AE) reports submitted to the regulatory agency database, as well as literature reports and other sources, including social media. Under the new EU legislation, Regulation (EU) 2019/6, reliance on signal management in pharmacovigilance activities is increased.

In addition, submission of adverse event data is increasing year on year. Changes in UK and EU legislation due to be implemented within the next two years will result in more adverse event reports being submitted to VMD. The quantity of data is also increasing due to the licencing of new and novel veterinary medicines; however the data submitted pre-authorisation is often limited, being based on relatively small studies. Post marketing safety data is required for identifying unknown risks, characterising risks and the use of drugs in real life, and to help prevent and minimise drug related risk.

The signal management process enables analysis of large volumes of data to provide assurance on the safety and efficacy of veterinary medicines. Pre-authorisation evaluation is limited in the ability to fully characterise the safety profile of a veterinary medicine. Signal management optimises finite resources and allows organisation and interpretation of large datasets of adverse events.

The pharmacovigilance team must keep pace with developments in this field and continue to provide a robust safety net of efficient and effective pharmacovigilance and reassurance to the end user and general public.

To support the use of signal management in the analysis of pharmacovigilance data, the VMD will look to:

[5] European Medicines Agency (2015) Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products. EMA/CVMP/901279/2011

- develop working relationships with other regulatory agencies, particularly those who have experience in handling and interpretation of large volumes of data.
- evaluate the methods and processes used for signal management in other regulatory agencies worldwide.
- develop best practice guidance and criteria for VMD signal management in partnership with other regulatory bodies and academia including accessing more than one dataset.
- establish a timeline and forum to discuss signals to determine regulatory actions.
- research and develop expertise to validate different statistical data mining methods for analysis of data and re-signalling.
- advance knowledge within the pharmacovigilance team of pharmacology and pharmacoepidemiology.
- enhance pharmacovigilance capability with VMD IT, developing and implementing further IT solutions for data analysis.
- interact collaboratively with industry to share methodology where appropriate including information from different datasets.

2.4.3 Improve the evaluation of environmental and residues adverse events

There is growing concern regarding the impact of pharmaceuticals in the environment, both in relation to their potential effects on ecosystems (e.g. dung fauna, pollinators) and effects on human safety (e.g. through contamination of water by hormones and antibiotics)[6]. Under veterinary medicines legislation, there is no requirement for routine surveillance of drug residues in the environment, and the reporting of environmental adverse events attributable to the use of veterinary medicines is rare. Therefore, in order to better understand the fate and potential impacts of chemical contaminants in the environment on biological organisms, further development of the process of how the VMD collates available environmental data is recommended.

Development of criteria to determine what constitutes a reliable pharmacovigilance signal for these types of events, the appropriate investigations and monitoring to be undertaken and effective regulatory action that subsequently could be applied, require further consideration.

Additionally, the environmental impact assessments carried out as part of the pre-authorisation assessment process for medicines for non-food-producing animals ends at Phase I. This is of concern as, without appropriate data on the fate and effects of such veterinary medicines, any potential impacts on the environment, resulting from their use, may be unidentified.

Whilst there is an established statutory system for monitoring residues of veterinary medicines in food products, reports of residues violations related to labelled use of

[6] European commission (2019) European Union Strategic Approach to Pharmaceuticals in the Environment. COM(2019) 128

products are rarely received through the pharmacovigilance system. Further evaluation of the signal detection methodology for such reports would help determine a possible need for review of withdrawal periods for associated products, ensuring the necessary level of consumer protection and food security.

In order to be assured of the safety of veterinary medicines and maintain expertise on current issues, more research and guidance on these topics are needed. Furthermore, this work will contribute to Defra's environmental objectives on promoting/maintaining biodiversity.

To improve the evaluation of environmental and residues adverse events, the VMD will look to:

- develop and/or extend working relationships with other government agencies and determine how they deal with environmental infringements (e.g. Environment Agency (EA) and Scottish Environment Protection Agency (SEPA)).
- research the effects of veterinary medicines on fungus/mycorrhizal networks.
- investigate the benefit-risk balance for compounds of environmental concern, such as endocrine disruptors, persistent, bioaccumulative and toxic substances (PBTs), and antimicrobials.
- understand the existing systems of environmental monitoring (of terrestrial and aquatic systems), for chemicals used as veterinary medicines in the UK.
- research and develop appropriate guidance on the risks of secondary exposure from household contamination, and exposure of bees and other pollinators, from topically administered veterinary medicines for companion animals.
- evaluate the need for post authorisation environmental monitoring programmes for those compounds considered to be a high risk to ecosystems.
- develop guidance on response to environmental and residues reports.

2.4.4 Strengthen risk management and risk minimisation approaches

A veterinary medicinal product is authorised based on data generated on a limited population of animals in a protected scientific environment. It is accepted that not all risks will have been identified at the time of authorisation and many will only be discovered or fully characterised post authorisation. This is particularly true for novel therapies, where adverse reactions cannot be predicted based on knowledge of the mode of action or the clinical data generated, and for products authorised under 'exceptional circumstances' to cover an, as yet, unmet clinical need.

Increased use of risk management plans (RMPs) could allow these novel products and those authorised under 'exceptional circumstances' to gain more rapid market access, whilst the missing information on the safety profile are generated in the wider population. RMPs describe what is known, and not known, about the safety profile of the medicine and summarise the safety concerns. The pharmacovigilance plan details how these safety concerns will be further identified and characterised,

whilst the risk minimisation plan describes measures to minimise and mitigate the risks where possible. Post-authorisation surveillance studies (PASS) can also form an important part of a RMP.

RMPs are a potentially valuable tool, routinely implemented for human medicines; however, more experience needs to be gained in the veterinary field on how they may be used to identify and minimise risks. There is currently limited guidance on the design and the appropriate statistical methods to be used when preparing and implementing, or when reviewing and amending, a RMP throughout the life cycle of a product. This requires us to address, for example; identification of products where an RMP could be considered, setting out the minimum standard for the design and content of a RMP, and clarifying the regulatory approach.

The effectiveness of risk management measures may only become apparent through pharmacovigilance and further research into their optimal communication to end users of medicines could be valuable. A more quantitative approach may be useful post-authorisation, to aid consistency and transparency in the re-evaluation of benefit-risk in the presence of new data.

To strengthen risk management and risk minimisation approaches, the VMD will look to:

- review how risk management plans and risk minimisation measures are planned, implemented, and regulated in other agencies, drawing on the experience of colleagues at the MHRA and in other regulatory authorities.
- further investigate the potential for the application of RMPs in the veterinary field, with a particular focus on innovative products and areas of unmet clinical need.
- identify any gaps in our scientific knowledge that require addressing through further training.
- build relationships with experts in the relevant fields (e.g. academia, other regulatory authorities).
- develop new guidelines and required standards for post-authorisation data collection and analysis within the context of a RMP.
- promote a regulated approach to marketing authorisation holder risk minimisation measures implemented during the post-authorisation phase.
- request feedback from stakeholders on the proposals.

2.4.5 Utilise big data in post-authorisation benefit-risk assessments

On-going benefit-risk evaluation is a core activity of pharmacovigilance and is based on accumulating evidence during the life cycle of a product; for example, from PSURs, signal detection, RMPs, scientific literature and even social media. However, better systems are required to assure the public about the safety of veterinary medicines. The total burden of adverse drug reactions (ADRs) across many millions of drug exposures, each of which has a small risk, has massive health, environmental and economic impacts. No matter the source, the quality of the data is very important and directly affects our decision on the best action; which may be issuing an immediate warning or pursuing further active investigation.

Risk assessment methodologies have evolved immensely, and this has an impact on the benefit-risk analysis evaluation. However, computational problems in risk analysis are often challenging, since there may be little or no empirical data available for some variables. Therefore, it may be necessary to employ subjective information from the analyst's judgment or expert opinion.

Assessing the causality of the risk is the core aspect of the benefit-risk assessment and depends upon the nature and the amount of evidence supporting an attribution hypothesis, relying on probabilistic evidence alongside multifactorial causality association (application of Bradford-Hill Criteria[7]) and collaboration (networking).

New strategies are required to connect researchers, datasets, biomedical knowledge and analysis algorithms, allowing VMD to fully exploit the true value behind state-of-the-art pharmacovigilance efforts. In the future, non-conventional sources of data, including big data[8], could be an important part of the benefit-risk assessment.

To utilise big data in post-authorisation benefit-risk assessments, the VMD will look to:

- consult other organisations and institutions (e.g. poison centres, insurance companies) to understand how big data are handled in other scenarios.
- undertake work-sharing assessments and utilise expertise in other fields, such as pharmacology, pharmacoepidemiology, and statistics.
- use suitable communication methods for those who need the information, e.g. end users and veterinary health professionals, in order that appropriate decisions are made, and actions taken, to assure animal and public safety.
- clarify industry requirements in legislation and/or guidance.

2.5 Facilitating the use of Novel Scientific Models and Tools

Pharmacometrics is the science of interpreting and describing pharmacology in a quantitative fashion[9]. It involves the use of pharmacokinetic and pharmacodynamic models, and application of mathematical and statistical methods to characterise, understand and predict the behaviour of a drug *in vivo*.

The use of such techniques and other novel scientific models and tools will aid efficient drug development and/or regulatory decisions and help replace and reduce the use of animals in experimental studies.

2.5.1 Increase application of pharmacological methods to support 3Rs

Scientific communications frequently refer to pharmacological methods to replace, reduce or refine the use of animals in research, and they are increasingly used in

[7] Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 58 (5): p.295–300

[8] Martin-Sanchez F. & Verspoor K. (2014) Big data in medicine is driving big changes. *Yearb Med Inform* 9 p.14-20

[9] Ette, E.I. & Williams P.J. (ed.) (2007) *Pharmacometrics: The Science of Quantitative Pharmacology.* New Jersey: John Wiley & Sons

studies submitted in support of marketing authorisation applications. Some 3Rs methodologies, such as use of the biopharmaceutics classification system (BCS)-based biowaivers and pharmacokinetic-pharmacodynamic (PK-PD) modelling in dose finding, have already been incorporated into scientific guidelines. Use of physiologically based pharmacokinetic (PBPK) models is mentioned in guidelines for human medicines and has been used in place of certain data in residues files for veterinary medicines.

Consideration of 3Rs approaches in regulatory testing of veterinary medicines is a requirement under Directive 2010/63/EU and the UK Animals (Scientific Procedures) Act 1986. Applicants should be encouraged to not only consider the principles of the 3Rs during the design phase of all studies, but also develop new 3Rs methodologies. However, it must be ensured that use of 3Rs methodology will provide equivalent assurance of quality, safety and efficacy as the current widely accepted methodology.

New 3Rs methodologies will provide increased opportunities to limit animal testing in support of marketing authorisation (including in the batch release testing of immunological products) and maximum residue limit (MRL) applications, through *in silico* and *in vitro* approaches, or methodologies that require the use of fewer animals (e.g. PK-PD modelling studies in place of classical dose determination studies). Where reducing the number of animals required is not possible, consideration should be given to opportunities for the use of surrogate endpoints and/or maximising the amount of data derived from a study.

In addition to animal welfare benefits, these approaches will reduce the costs associated with the development of veterinary medicines, with the potential benefit of increasing veterinary medicine availability.

To increase the acceptance of pharmacological methods in the 3Rs context, the VMD will look to:

- review current scientific guidelines and identify opportunities for 3Rs implementation.
- promote the use of new 3Rs methodologies by providing greater clarity through the development of new guidelines. These will clarify the likelihood of acceptance of using established (e.g. BCS-based biowaiver) and novel approaches to fulfil data requirements and the means by which such approaches should be validated.
- interact collaboratively with industry to focus development on areas for 3Rs.
- build relationships with experts in the relevant fields (e.g. academia, other regulatory authorities).
- identify training resources for established/novel approaches (e.g. PBPK modelling).
- explore opportunities for funding R&D projects related to the development of 3Rs methodologies.
- offer scientific advice for applicants relating to the acceptability of their proposed method.

2.5.2 Enable utilisation of statistical modelling and simulation techniques

Models are simplified representations of a system. Although modelling is subject to limitations because of the potential uncertainties with the sampled data and the potential lack of validity for some of the parameterisation supporting the models, it remains the case that they can be successfully used to predict outcomes under different assumptions. As a result, various modelling techniques are employed as part of the decision-making process during the authorisation of veterinary medicines.

In particular, modelling and simulation approaches can make efficient use of imperfect empirical datasets and are already used in pharmaceutical development to predict pharmacological and toxicological effects. Although the potential benefit of using models is clear, it is important that regulators and stakeholders have a good understanding of how they are developed and validated, if they are to be more widely used and accepted in the regulatory arena.

Pharmacological modelling

Within a population, the effect of an active substance can vary markedly from one individual to another, including between animals in laboratory-based dose determination studies and those in field trials. A potential source of this variability is differences in the pharmacokinetic profile of the active substance between individuals. Factors that have been reported to influence pharmacokinetics include age, gender, disease status and genetics. Population pharmacokinetics (PopPK) can be used to refine dosage regimens using pharmacokinetic data from individuals, which are more closely representative of the target population (e.g. if the animals used in laboratory studies have markedly different demographics and/or disease status to those that will be treated in the field), or to support dosing recommendations for specific sub-populations (e.g. with regard to age, gender). The result is an improvement in the product information available for end users. Whilst not obligatory, such an approach should be encouraged.

Clinical aspects

Applications for marketing authorisations often rely either partially or fully on non-proprietary data, including published literature and expert testimonial/review. Improvements in the ability to collect, collate and analyse big data have more recently led to the establishment of large databases which can be interrogated and sampled to help answer specific research questions (e.g. SAVSNET, VetCompass). The VMD also has access to large amounts of data from previous applications. There may be ways in which these data could be collated and analysed. In some cases, there may be potential for such data to be utilised by the pharmaceutical industry and regulators to reduce the number/size of *in vivo* studies (e.g. dose determination, confirmation or even field studies). However, concerns regarding data ownership/confidentiality need to be addressed.

Technological advancements are leading to rapid expansion of the type and volume of animal health data which can be collected. Examples include the sensor/wearable technology industries, whereby observations can be made more frequently, and large datasets can be rapidly collated/analysed. There is also significant expansion of the '-omics' technologies. Many of these new data sources may be of use in applications for marketing authorisations. From a regulatory perspective, guidance is needed as to how these novel datasets could be presented by applicants and assessed by the VMD.

Modelling in toxicology

The use of modelling for the derivation of toxicological reference values (TRVs) and point of departures from toxicity studies is becoming widely accepted and is encouraged to replace the use of other TRVs, such as no observed (adverse) effect level (NO(A)EL) and lowest observed (adverse) effect level (LO(A)EL). The benchmark dose (BMD) approach is a very useful tool for this purpose, and various associated software are already publicly available. It is important for regulators and stakeholders to understand how these models work, and further, to identify how they can be used to optimise study designs, to make the best use of the data, and to promote the 3Rs approach for reducing animal testing.

Environmental modelling

Modelling techniques are extensively used in the environmental risk assessments for veterinary medicines (e.g. BathAUTO, Depomod, Intermediate Dynamic Model for Metals and FOCUS). Such models are used to predict environmental exposure, of the aquatic and terrestrial compartments, to potential chemical contaminants resulting from use of veterinary medicines. These models can be extremely complicated due to the complex nature of the environment, and because most of these models have a dynamic component, requiring them to model multiple inputs covering decades or even hundreds of years. Furthermore, accessibility and transparency are issues, as the models tend to be bespoke and similar to a ‘black box’. Some of these models have been criticised for not being representative of what they are modelling and for not being accessible. Guidance is required as to how to appropriately evaluate the models and ensure that environmental impacts are appropriately considered. This work will contribute to Defra’s environmental objectives on promoting/maintaining biodiversity.

Consumer safety

Statistical modelling is currently used in the calculations of withdrawal periods. However, the methodology requires refinement and improvement. The calculation of withdrawal periods for products used in dairy animals during the dry-off period is one example where modelling can be used to improve the withdrawal period calculation and avoid overestimation for animals with short dry-off periods.

Pharmacological modelling (see above) can also be used to refine the default inter- and intra-species factors that are commonly used for the derivation of acceptable daily intakes (ADIs).

To enable utilisation of statistical modelling and simulation techniques, the VMD will look to:

- identify appropriate simulation and modelling techniques and collaborate with experts/other frameworks/industry to gain a greater understanding of these techniques, to see if they can be made more accessible and transparent, and to evaluate their merit for the authorisation of veterinary medicines.
- interact with industry to encourage the use of new modelling techniques to make better use of data and reduce the number of animals used in testing.
- investigate the potential to incorporate big data and novel data sources into the current marketing authorisation framework.

- collaborate with experts/industry to explore potential sources of data, analytical approaches and whether the data could be used alongside, or in place of, more traditional data sources, for the purposes of a marketing authorisation application.
- ensure that assessors are fully trained in these advancements and that appropriate guidance is provided for both regulators and industry.

2.6 Ensuring Access to High Quality Regulatory Scientific Expertise

Innovation in veterinary medicinal products to prevent and treatment disease is developing quickly. Medicines are becoming more complex both in terms of the preventative or therapeutic agent and also the delivery system. This diversity of technology and innovation means that scientific assessors need to continuously develop their skills and expertise and identify and fill any knowledge gaps to be able to successfully deal with these new types of veterinary medicines.

The VMD is determined to ensure it maintains its scientific expertise and capability, and has ready access to specialised skills and competencies. This will enable us to continue to provide high quality scientific advice and undertake appropriate high-quality critical review and benefit-risk assessment of applications for new veterinary medicines.

To ensure the necessary access to regulatory scientific expertise and capability, the VMD will look to:

- strengthen existing links between the VMD and other regulators and leverage collaborative links with new global/international regulatory partners, to:
  - provide access to a wide range of scientific assessors with different experience and expertise and to share our knowledge.
  - provide exposure to different types of medicines and products to maintain and extend VMD expertise.
  - enable mutual scientific peer review.
  - identify better, smarter ways of working.
- attract and retain highly qualified and skilled staff by:
  - providing training and professional development opportunities.
  - offering secondments and experience postings to external organisations to gain expertise and grow networks, e.g. the Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (OIE) and other regulatory bodies.
- develop a network of independent scientific experts by:
  - identifying individuals/groups with recognised scientific expertise.
  - establishing an efficient mechanism whereby the VMD can procure advice in a timely manner.

    - participating in relevant scientific and expert working groups, using the UK's independent status to seek autonomous membership of committees and advisory groups.

- work with academia to address emerging regulatory scientific issues, ensuring the focus of the VMD R&D programme remains current and is used to commission work on scientific questions of greatest importance and relevance.