VETERINARY MEDICINES AND ANTIMICROBIAL RESISTANCE EVIDENCE PLAN 2011/12

Evidence Plans are part of Defra's business planning processes. They have been developed for each policy programme, ongoing function or hub with a substantial evidence base

The main purposes of Evidence Plans are to help Defra policy and evidence teams to:

- Maintain a clear 'line of sight' between policy objectives and evidence needs;
- Ensure best use of others' evidence and maximise opportunities for partnerships;
- Show a clear rationale and value for money for Defra investment in evidence;
- Prepare for policy evaluation.

1. POLICY RATIONALE

1.1 Policy context

Preamble

This document sets out the evidence plan for both the veterinary medicines and antimicrobial resistance (AMR) research programmes. The policy lead for AMR is currently shared between the Veterinary Medicines Directorate (VMD) and Defra FFG (VST [Veterinary science team]: DMCES [Disease Mitigation, Control and Export Support]) and there is close collaboration on this work. Ministerial agreement was received on 10th January 2011 to transfer all AMR policy responsibility to the VMD. The policy for veterinary medicines is already the sole responsibility of the VMD.

Defra's AMR Senior Reporting Officer (SRO) asked that these two evidence plans be created in a combined document so that linkages between the two programmes could be identified. In providing a single evidence programme for the two research programmes, it is worth noting the differing scope of each. The AMR evidence described below is for FFG (VST: DMCES). The Veterinary Medicines research programme is used to provide evidence to support a broader range of policy issues relating directly to the use of veterinary medicines, which includes related AMR. Thus the complementary aspect of the two programmes is AMR and the other evidence secured with the Veterinary Medicines research underpins the broader aspects of all veterinary medicines policy.

Thus in providing an amalgamated evidence plan for AMR and Veterinary Medicines a degree of repetition is unavoidable in what follows.

Veterinary medicines evidence to underpin VMD's policy

UK and EU legislation, which aims to ensure that veterinary medicines can be used safely and effectively, is administered in the UK by the VMD. The VMD's main aims are to protect public health, animal health and the environment and promote animal welfare by assuring the safety, quality and efficacy of veterinary medicines. The VMD also aims to ensure the continuing availability of veterinary medicines and seeks to improve their availability.

The rationale for funding research in these areas is to underpin an effective authorisation

and control system, which not only protects and promotes animal health and animal welfare but also to protects those using or coming into contact with veterinary medicines either directly or through residues in food. The authorisation process also seeks to protect the aquatic and terrestrial environments by ensuring that there are no unacceptable short or long-term harmful effects arising from the use of veterinary medicines.

Increasingly, best practice principles are viewed as a means to ensure the continuing availability of veterinary medicines, particularly for those which are authorised but where resistance is known to be a potential issue threatening efficacy. It is important that best practice principles are demonstrated to be effective using appropriate scientific evidence. The VMD's primary concerns are antimicrobials, anthelmintics and bee medicines.

As immunological products cannot be fully defined in the same way as pharmaceuticals, monitoring the continued acceptability of the quality control of veterinary immunological products is best achieved by undertaking research to increase the safety, quality and efficacy of the quality control tests through the setting of appropriate standards.

Studies designed to support investigations into alternative treatments may also be supported where animal welfare is of concern and the market is too small to support the full independent development of new products.

Antimicrobial resistance (AMR): progressed jointly by VMD and core Defra FFG (VST: DMCES)

The guiding principle of Defra's policy, with respect to antimicrobial resistance, is to seek to reduce the impact of antimicrobial resistance in organisms associated with animals on public health and animal health and welfare in a proportionate way, in conjunction with partners and in accordance with the GB Animal Health and Welfare Strategy.

Defra and VMD together work with the Food Standards Agency, the Health Protection Agency and the Department of Health in the work on antimicrobial resistance, as well as with colleagues in the Scottish Government, Welsh Assembly Government and Department of Agriculture and Rural Development in Northern Ireland.

Evidence to support risk-based decisions in developing, implementing, and evaluating antimicrobial resistance policy is obtained through the collection of some limited targeted and scanning surveillance data, assessment of the implementation of specific control measures, collaboration and knowledge sharing with colleagues in human health and the outputs of targeted research projects. This provides a scientific evidence base that helps inform antimicrobial resistance risk assessment and policy direction in Great Britain (GB) and for negotiating risk-based, proportionate EU-driven antimicrobial resistance objectives.

Overall, the antimicrobial resistance policy area supports the aims of the Animal Health and Welfare Strategy for Great Britain in relation to protecting public health, protecting animal welfare and the wider society (which includes biodiversity, the environment and the rural economy).

As antimicrobial resistance continues to develop and spread and it will be of increasing

concern in both medical and veterinary terms. The end point could be that antimicrobial resistance becomes so widespread that we return to the situation that existed in the1920s where what are currently curable diseases could not be cured and many people and animals died or were chronically ill. This is compounded as once a specific type of resistance has developed it is extremely difficult to eradicate it. This combination means antimicrobial resistance could ultimately also be deemed one of Defra's (and the Department of Health's) big challenges. Any issue with such profound long term consequences warrants appropriate research and surveillance and as many measures implemented as possible to mitigate as far as possible the speed with which this situation becomes the status quo. Therefore it is strongly recommended that additional funding to enhance our understanding and to inform our policy direction is now considered.

2. CURRENT STATE OF KNOWLEDGE, INVESTMENT AND FUTURE REQUIREMENTS

2.1 Current state of knowledge

Please also annex key references.

Veterinary medicine (VMD)

VMD has access to extremely detailed dossiers of evidence submitted to them for each veterinary medicine for which a pharmaceutical manufacturer has sought a UK marketing authorisation. VMD also has access to similar data submitted for approval for European marketing. Marketing authorisation considerations conducted by the VMD can be for single country (i.e. UK) only, a group of EU countries or for the entire EU. Conversely VMD has little or no information on any other possibly useful treatments. Farming practices and disease patterns within the UK may be different from elsewhere thus necessitating a need for evidence to develop policy for control of specific diseases whilst minimising the risks to those administering treatments and minimising the impact on the environment.

Whilst chemical contaminants in food and animal health and treatments are of great international interest, the factors influencing them vary considerably from country to country. Where overseas data exist these may not be available or directly applicable to the UK consumer or animals. In many cases data do not exist and it is necessary to generate the information required in order that national safety assessments can be made in the UK. This is true not only for surveillance activities but also for the related research activities required to support the full range of work at the VMD. Where possibilities exist for collaborative research, such as in the development of analytical methods in support of surveillance, it is necessary to ensure that the UK can contribute fully through its research programme. The UK, through the VMD, actively participates in a number of international fora, e.g. the Codex Committee on Residues of Veterinary Drugs in Food which sets international standards for veterinary medicine (Maximum Residue Limits) which are binding on the EU if the EU does not raise scientific objection to adoption of the standards proposed. Evidence generated in the VMD research programmes underpins UK input to such discussions.

Information is collated from the scientific literature and the companies marketing

products containing substances of interest (subject to commercial confidentiality). This is assessed prior to recommending or embarking on any studies.

Antimicrobial resistance (AMR): progressed jointly by VMD and Defra FFG (VST: DMCES).

AMR represents an increasing threat to both human and animal health. Some types are reasonably well understood (e.g. MRSA- meticillin resistant *Staphylococcus aureus*), others have developed more recently and have now been identified and have begun to be characterised. Further resistance mechanisms and resistant micro-organisms will continue to evolve whilst selective pressure is applied.

This selective pressure is primarily the use of antimicrobial products (such as antibiotics, disinfectants etc) but as micro-organisms can carry their AMR genes with others that also enhance survival (such as the ability to remain viable in the presence of heavy metals) then even if all use of antimicrobial products ceases the resistance genes are likely to be maintained in the microbial population for an extended time period. Increasingly, farming practices are also being considered as additional drivers for the development of AMR.

Antimicrobial resistant micro-organisms may develop or acquire resistance to one or a number of antimicrobials. Many micro-organisms can now routinely be multi-drug resistant (termed MDR). Antimicrobial resistant micro-organisms may be found in various situations, including in people, animals, foods and in the environment (including in wildlife, watercourses, soil etc). The following areas are important to enhance our understanding of both the potential human and animal health impacts of antimicrobial resistance:

- How these different microbe populations interact,
- Whether resistance can be passed between different species of micro-organism as well as being shared within the species,
- The prevalence of the various resistant organisms in the various situations (and AMR genes where these can be easily passed between different species of micro-organism)
- The selective effect different antimicrobials may exert, and
- What methods may be successfully applied to stop or mitigate the selective pressure.

Understanding these types of issues for each type of AMR requires research and surveillance focussed on each type of resistance. For longstanding types of resistance (e.g. MRSA which was first identified after the introduction of penicillin in the early 1960s) more is generally known, but fundamental issues concerning strains such as MRSA ST398 which have appeared in Europe in both pigs and pig stockmen are not yet understood.

Our knowledge base is not just dependant on how long it is since a new form of resistance was first identified, but also on the threat presented by the micro-organism or type of resistance. Some microbes invariably cause illness (sometimes this can be very serious or fatal). Others can cause disease on occasion but in other situations may merely colonise an individual (this is often the case with MRSA). Some micro-organisms can infect just people or just animals, whilst others can be passed from animals to

people (and vice versa; these are termed zoonoses). A microbe that does not itself cause disease may still warrant research or surveillance resource as it may in future share its resistance mechanism with other microbes that do cause disease. Equally, if a disease-causing micro-organism (these are termed pathogens) does not require the use of antimicrobial products to control it then this means there is less reason to investigate, as even if it acquires a type of antimicrobial resistance this won't affect the overall clinical outcome.

These factors mean that current knowledge about different types of resistance varies considerably and continued use of antimicrobial products and the development of new ones means new forms will continue to arise as a consequence of this selective pressure. Current Defra R&D and surveillance efforts are therefore focussed on types of antimicrobial resistance and micro-organisms of potentially highest impact for public and animal health. A vast resource would be required to obtain the same understanding of every micro-organism/resistance combination. Increasingly it is acknowledged that farming practices may drive the development of antimicrobial resistance and, by comparing and contrasting farming practices, information will be generated to demonstrate whether the rate of development of antimicrobial resistance can be influenced by changes in farm management.

2.2 Primary objectives of evidence activities

Veterinary medicines

Veterinary medicines, including antimicrobial products, play a key role in maintaining and improving animal health. These will potentially have an impact on human health by ensuring zoonotic diseases can be successfully treated, through the presence of residues, and the change in selective pressures for antimicrobial resistance. The following paragraphs fully address the concerns and key Defra Business Plan priorities identified above.

Veterinary medicines are required to treat and prevent disease in animals, thereby minimising animal suffering. In addition, they are fundamental to ensuring a competitive, sustainable and thriving food production sector, together with a growing public concern for companion and other animals, reflecting the perceptions of the "big society".

The five principal objectives of the veterinary medicines R&D programme are the development of:

- alternative methods to replace or reduce animal testing in the development and manufacture of veterinary medicinal products;
- appropriate methods to assess potential impacts on terrestrial and aquatic environments arising from the use of veterinary medicines;
- effective residue testing methods in line with national and EU statutory requirements;
- strategies to minimise the development of resistance to veterinary medicines to ensure continuing availability; and
- appropriate methods to better understand the long-term health effects on man and animals coming into contact with veterinary medicines.

VMD relies on evidence to ensure the safety, efficacy and quality of medicines authorised for use in the UK. These veterinary medicines not only safeguard animal health but they are also the means to prevent and treat potentially fatal zoonotic infections that threaten people. Residues of veterinary medicines can affect both human consumers of animal products and the environment through their excretion post administration to the animals. VMD maintains a strict evidence based pre-market authorisation process and post administration statutory residue monitoring programme and suspected adverse reaction surveillance to ensure minimal potential for animal, human and environmental impact following the use of the medications according to authorised usage.

Antimicrobial resistance (AMR)

Antimicrobial resistance is an evolving area. Defra's particular concerns are the possible transfer of antimicrobial resistance genes and resistant organisms between animals, humans and the environment and the development of significant reservoirs of resistant bacteria in animals.

It is important therefore to develop effective mechanisms for identifying, collecting and interpreting the information that will detect relevant developments concerning antimicrobial resistance in micro-organisms in animals.

Similarly it is important that the mechanisms that select for the development and spread of AMR are well understood, the best means to mitigate the transmission of AMR genes and organisms are identified, and how the potential public and animal health and welfare impacts can be minimised.

AMR R&D is focussed on five main areas:

- Developing appropriate tools for AMR detection and characterisation
- Investigation of how mutations/acquired resistance develop and are transferred
- Qualitative risk assessments
- Spread/transmission of AMR genes and/or host bacteria
- Options for prevention and control of AMR.

New AMR surveillance and research will be prioritised based on the reasons for Defra intervention as set out in the GB Animal Health and Welfare Strategy. The strategy foresees intervention by Defra to:

- protect public health,
- protect and promote animal welfare,
- protection of the wider society (including biodiversity, sustaining existing ecosystems and the potential impact on farming's economics and sustainability) and
- potential impact on international trade.

The key evidence gathering activities provided by the surveillance and research that help inform antimicrobial resistance policy objectives are:

- identifying new and emerging forms of antimicrobial resistance in the animal

population and monitoring all *Salmonella* isolates (one of the key zoonoses)

- using collaboration with other projects as a means to increase our understanding of antimicrobial resistance in specific micro-organisms, e.g. Campylobacter and *E. coli* isolates obtained from poultry and working in partnership with colleagues in other Government departments across the UK to enhance our evidence base and access to expertise.
- assessing the impact of medicine usage on the development of resistance to help develop responsible use guidelines in conjunction with the Responsible Use of Medicines in Agriculture (RUMA) Alliance and across the EU.

The current Defra-funded programme of research looks at alternative (i.e. not chemical based) methods of controlling endemic diseases. Key themes within the programme are the development of sustainable control methods, especially vaccine-based approaches and the development of diagnostics. We are also focussed on working closely with industry and academia to ensure research is both cutting edge and applicable to the UK situation. This is also key to maintaining nuclei of expertise within the UK which can be called upon in the event of future risk to human and/or animal health from a micro-organism that has acquired resistance to antimicrobials.

2.3 Current investment in evidence

Veterinary medicines, including antimicrobial resistance

The overall evidence budget for veterinary medicines (including antimicrobial resistance) in 2011-12 is £2,461,500 of which £2,158,000 is for R&D and £303,500 is for surveillance for certain aspects of antimicrobial resistance.

2.4 Identifying and prioritising new evidence needs

Veterinary medicines (VMD)

All the above topic areas (section 2.2) are fundamental to providing the VMD with the evidence base from which to develop policy on veterinary medicines for the UK and to permit these medicines to be authorised for use in the UK. During the course of routine work and also when questions are raised relating to the work of the VMD, topics for R&D to assist in the work will be identified. The VMD does not assign fixed proportions of the available budget to particular topic areas but rather it assesses specific policy needs and assigns priorities within the programme on an annual basis, taking advice from the VMD R&D Steering Group.

Antimicrobial resistance (AMR)

Antimicrobial resistance surveillance concerning zoonotic pathogens warrants a higher priority than that related to microbes that do not cause disease or are not zoonotic. Ease of transmission and whether other control methods (e.g. cooking and kitchen hygiene) are effective will also influence our decision making. In addition EU requirements to undertake AMR surveillance will also influence the AMR surveillance that is undertaken. New and emerging resistance mechanisms require an appropriate level of investigation if identified in the UK.

The success of controls that policy imperatives determine should be deployed must also

rely on an appropriate surveillance system so that the effectiveness of controls can itself be monitored.

Review of R&D to identify and prioritise new evidence needs

Robustness of R&D evidence on veterinary medicines and antimicrobial resistance is assured by peer-review of research proposals prior to commissioning and by periodic review of the R&D programmes controlled by the VMD and Defra covering veterinary medicines and antimicrobial resistance.

The purpose of the reviews is to:

1. Evaluate completed and current research projects in relation to their scientific quality, usefulness to policy and contribution to the evidence base, and delivery of the overall objectives of the programmes.
2. Assess the size, scope and balance of the current programme in relation to current policy needs.
3. Consider the future direction of the R&D programme and identify future priorities, taking into account the size, scope and balance of the current programme as well as research funded by other sponsors.

In addition to enhancing the understanding of veterinary medicines as a whole, another knowledge gap is how best to communicate with both veterinary surgeons and animal keepers (farmed or domestic animals) in a way that effects beneficial behavioural change. More social science research is therefore required.

2.5 Secondary benefits of evidence activities

Veterinary medicines, including antimicrobial resistance

The research covered by this programme will complement the work carried out by other Animal Health and Welfare Evidence Programmes including aquatic animal health, bovine TB, exotic disease, new and emerging diseases and their control and treatment (taking into account where necessary the economic benefits to be gained for the farming and companion animal sectors), public health protection, veterinary surveillance and other studies on the medical and environmental effects of the use of veterinary medicines.

Collaboration with Defra science and policy groups (and other Government departments both in the UK and internationally) will be maintained inside and outside a range of advisory groups including the VMD R&D Research Programme Steering Group, the Defra Antimicrobial Resistance Co-ordination group, and the independent advisory groups such as the Veterinary Products Committee and the Veterinary Residues Committee. Ongoing liaison with Research Council interests is provided by the Defra FFG Veterinary Research Unit. These initiatives will ensure effective co-ordination with Defra interests and avoid duplication. Joint project support will be encouraged whenever possible. Pooling of resources, such as jointly supporting research needs on antimicrobial resistance, as discussed below, is seen as a particular strength and ensures that the most important areas are identified and supported whilst avoiding duplication of effort.

The programme also supports the Horizon Scanning Programme by identifying and

assessing the risks and possible future threats that the development of new veterinary medicines may have on Defra's objective to protect public health and ensure high standards of animal welfare. It will also seek to develop new and more efficient methods for the detection of residues of veterinary medicines and mechanisms of antimicrobial resistance to support the surveillance programmes co-ordinated by the VMD and Defra.

Both VMD and Defra hold meetings with interested parties (such as the VMD annual open meetings, Defra meeting with poultry industry to explain new AMR surveillance findings, and Defra's facilitation of the 1st and 2nd International MRSA Conferences, both targeted at the international scientific community).

2.6 Alignment to long-term evidence challenges and Defra Business Plan objectives

Priorities and responsibilities

Defra's veterinary medicines and antimicrobial resistance evidence programmes will support decisions made to further all three of Defra's key Business Plan priorities (and one of the additional major responsibilities) which are:

'Support and develop British farming and encourage sustainable food production'

- Help to enhance the competitiveness and resilience of the whole food chain, including farms and the fish industry, to help ensure a secure, environmentally sustainable and healthy supply of food with improved standards of animal welfare

'Help to enhance the environment and biodiversity to improve quality of life'

- Enhance and protect the natural environment, including biodiversity and the marine environment, by reducing pollution, mitigating greenhouse gas emissions, and preventing habitat loss and degradation

'Support a strong and sustainable green economy, resilient to climate change'

- Help to create the conditions in which businesses can innovate, invest and grow; encourage businesses, people and communities to manage and use natural resources sustainably and to reduce waste; work to ensure that the UK economy is resilient to climate change; and enhance rural communities responsibilities

A fourth area that, although not one of the three Defra Business Plan key priorities, is also a key aim for Defra is to:

'Prepare for and manage risk from animal and plant disease'

- Protect the environment, society and the economy from the risks of animal and plant disease through a range of controls, surveillance and horizon-scanning activities that help us understand the risks and maintain proportionate management responses

The evidence relating to veterinary medicines and antimicrobial resistance gathered by the VMD and Defra is intrinsically linked to all three of the big challenges identified in the

Evidence Investment Strategy (climate change, a sustainable food supply and protecting ecosystems) and is fundamental to the three key Defra Business Plan priorities and one of the other major responsibilities as set out above. The paragraphs below set out just how these topics relate to these strategically important areas for Defra.

The research programmes will directly support Government policy to protect public and animal health, food and the environment. This complements the work carried out by the Department of Health and the Food Standards Agency. Already successful efforts to establish and extend collaborative and jointly-funded research between other government Departments and interested institutions in the UK as well as within and outside Europe (e.g. collaboration with the US FDA to detect abuse of antivirals used illegally to treat avian influenza in poultry) will continue to be promoted and developed.

In terms of linkage to the climate change work many of the means of lessening the impact on climate change of agriculture relate to farmed livestock and revolve around increasing intensification and improving productivity (partly via reducing endemic disease) to reduce absolute animal numbers and so green house gas impacts. However increasing intensification also increases disease spread and so the impact of endemic disease and can mean more vaccines and veterinary therapeutics will be required to keep farmed animals healthy and productive and safeguard the health and welfare of companion animals. The more antimicrobial and anthelmintic medications are used the higher the selective pressure for new forms of resistance to develop and spread, to the ultimate detriment of both animal and human populations. Therefore a properly informed understanding of the effects of these climate change initiatives is required, and this is reliant on a suitable breadth and depth of research and appropriate surveillance to identify trends.

The sustainability and economics of the animal-derived food supply may also be compromised by the development of resistance to existing veterinary medicines. The impact of antimicrobial resistance will be affected by food preparation as some food preparation techniques will kill resistant micro-organisms just as effectively as non-resistant ones. Another aspect of antimicrobial resistance that could ultimately have a significant consequence is the widespread use of disinfectants etc in food preparation. Resistance can also develop to these products, again potentially disrupting the long term sustainability of particular food types and preparation and supply routes.

Antimicrobial resistance also threatens to compromise Defra's aim to protect ecosystem services. Resistant micro-organisms are readily shared between people, animals and the wider environment. There is already clear evidence of antimicrobial resistant micro-organisms in wildlife populations (such as that published identified in gulls in Portugal) and similar findings in wildlife made by the VLA when investigating emerging types of resistance on English farms). It appears likely (although unproven) that a particular type of resistance in *E. coli,* first identified by the VLA in Great Britain in cattle during 2004 following its arrival in the human population some years earlier, may have been, in part, spread to animals via the spreading of sewage sludge on to pasture. Resistant organisms can also be transmitted via water and so there is scope for existing ecosystems to become colonised by resistant organisms over time and to act as a reservoir through which both people and animals can become infected. Some antiparasitic veterinary medicines have already been banned to stop the disruption of specific ecosystems such as the unintended poisoning of aquatic invertebrates, drawing on evidence from the VMD R&D programme.

As antimicrobial resistance continues to develop and spread and it will be of increasing concern in both medical and veterinary terms. The end point could be that antimicrobial resistance becomes so widespread that we return to the situation that existed in the1920s where what are currently curable diseases could not be cured and many people and animals died or were chronically ill. This is compounded as once a specific type of resistance has developed it is extremely difficult to eradicate it. This combination means antimicrobial resistance could ultimately also be deemed one of Defra's (and the Department of Health's) big challenges. Any issue with such profound long term consequences warrants appropriate research and surveillance and as many measures implemented as possible to mitigate as far as possible the speed with which this situation becomes the status quo. Therefore it is strongly recommended that additional funding to enhance our understanding and to inform our policy direction is now considered.

Veterinary medicines for bees and antimicrobial resistance are both new and emerging threats (and potentially exotic disease issues). There has been considerable recent public debate on the decline of the bee population in the UK and internationally. Bees are fundamental for pollination of crops and their loss is of highly significant concern to agriculture as a whole. A number of initiatives have been launched to consider this issue further and the VMD is actively involved in developing strategies to make medications more readily available for the treatment of bees against the parasitic Varroa mite and Nosema, a protozoal infestation.

Honey is generally considered to be both a natural and healthy food. However the use of veterinary medicines in bees can lead to residues in honey. There is currently no agreed international means of setting maximum residue limits for treatments used in bees producing honey. The VMD is leading an international effort at Codex Alimentarius to establish a protocol for how this might be addressed. In a similar way VMD needs to be ready to respond in an appropriate manner to other veterinary medicines issues as they arise, gathering and assessing appropriate scientific evidence to inform policy making.

3. INTERNAL CAPABILITIES - USING DEFRA'S EVIDENCE SPECIALISTS

3.1 Range of knowledge disciplines needed

Veterinary: to understand the need for treatment of animals, epidemiology of diseases being treated, assess possible alternatives and the role of husbandry in amending the treatment that may be required. Veterinarian's scientific skills are also necessary to understand microbiological and genetic background to antimicrobial resistance and to consider the potential benefits that proposed research and surveillance may bring and that it is appropriately designed to provide reliable results that will progress understanding and ultimately Defra's AMR policy.
Scientist: scientific skills are necessary for assessing veterinary medicine issues such chemists, pharmacists, toxicologists, environmental scientists and epidemiologists, and for antimicrobial resistance microbiologists, and other scientific skills as required to consider the potential benefits that proposed research and surveillance may bring and that it is appropriately designed to provide reliable results that will progress understanding and ultimately Defra and VMD's policy needs.

Social scientist: to understand the motivation for particular prescribing approaches by veterinary surgeons and factors that influence the types of treatment that animal keepers are willing to accept so that Defra's attempts to improve current practices by making them more responsible can be effectively achieved by guidance and education rather than legislation and enforcement.
Economist: to provide economic evidence on the potential costs of possible policies, and to inform impact assessments and cost/ benefit analyses required to progress policy goals.

The correct mix of skills has been achieved by in the main using skills already present in both the VMD and Defra. For some areas of concern (such as prescribing practices in specific branches of the veterinary community) we seek expert input from appropriate experts.

3.2 Access to internal specialists

VMD (Responsible for policy and delivery for veterinary medicines, including some aspects of antimicrobial resistance)

As stated above, the VMD is a specialist agency and has a pool of experts on which to draw as required.

Core Defra (FFG, VST: DMCES) (responsible for other aspects of antimicrobial resistance policy)

Veterinary surgeons lead on antimicrobial resistance policy as well as guiding the evidence requirements that are supplied by R&D, AMR surveillance and the investigation by VLA of new and emerging types of resistance that are identified via the scanning surveillance work that Defra undertakes on new and emerging diseases and which is discussed in the respective evidence plan. Few findings actively influence AMR policy direction so the majority of this time is science and evidence associated, rather than policy.

In addition to the specialist resource there is some policy resource. These individuals have roles dedicated to AMR policy work such as drafting briefings, responding to Parliamentary Questions and Deal With Officially correspondence, etc. and in acting as the secretariat for the MRSA sub-group.

3.3 Future resource needs and filling gaps in expertise

VMD (Responsible for policy and delivery for veterinary medicines, including some aspects of antimicrobial resistance

There are no obvious skill gaps in the staff within the VMD but resources are limited and there is a need to effectively prioritise workloads if all VMD obligations are to be met.

Core Defra (FFG, VST: DMCES) (responsible for other aspects of antimicrobial resistance policy)

Future core Defra extra skills required (and if source from VLA etc say so)
Key specialist needs are likely to remain veterinary for technical aspects, epidemiological for appropriate assessment of both outbreaks that are investigated and to ensure a robust statistically valid approach is taken in implementing both new R&D and surveillance, plus policy specialists, legal advisors, social scientists (if we are to avoid red tape and rely on voluntary uptake of good practice by vets prescribing antimicrobials and all those involved in administering them in all situations) and economists to help take forward legislative packages that underpin the control measures that are most appropriate. We will continue to make use of scientific specialists at VLA via the Contracts and Programmes that we fund, and to seek input and advice from the non-Defra experts involved in the Defra Antimicrobial Resistance Coordination Group and other experts that we already liaise with in deciding Defra's AMR policy direction. In fact our links through such bodies are not just with colleagues in other government departments but also with the key veterinary organisations dealing with various animal species, and also on a wider basis with RUMA (the Responsible Use of Medicines in Agriculture Alliance) and other organisations campaigning to reduce the veterinary consequences of antimicrobial resistance such as the Bella Moss Foundation. We will continue to look at resource sharing with core Defra colleagues on a VST wide basis.

4. EXTERNAL KNOWLEDGE SUPPLY AND PARTNERS

4.1 Strategic external capabilities and suppliers

VMD is required to meet statutory EU obligations for veterinary medicine residues surveillance. Three laboratories in the UK are designated as national reference laboratories for this purpose. The VMD depends on their scientific integrity, which is independently assured to meet international standards, and advice to assist with delivering the programme.

VMD relies upon AHVLA and VMD for antimicrobial resistance evidence. VMD's AMR contract funding of AHVLA directly funds purely AMR work. However, VMD also indirectly benefits in AMR terms beyond the actual contracted funding on AMR as it benefits from AHVLA's microbiological, epidemiological and statistical skills and resources beyond what the limited VMD AMR budget could achieve in isolation. Cost-saving measures that AHVLA may have to implement over the spending review period are likely to have some impact on AMR and VMD work. We will ensure that the CSA is informed of any issues resulting from reductions in budgets.

VMD works with experts based in the Department of Health and the Health Protection Agency, the Food Standards Agency and from partner organisations in Northern Ireland, Scotland and Wales. Some AMR R&D is contracted out by tender and while it is likely that non government labs will continue to bid for and receive funding for AMR research it is possible that more collaborative projects will be prepared in future as facilities become more limited.

4.2 Leverage and partnerships

The EU runs a Framework Programme for research which includes topic areas of relevance to the work of the VMD. This is closely monitored and collaborative funding provided to projects in key areas. In addition, research collaborations are established

with other government departments and agencies (both inside and outside the UK) whenever possible.

The Defra Antimicrobial Resistance Coordination (DARC) group (chaired by the VMD) includes members from a wide range of government organisations: Veterinary Medicines Directorate, Defra (Disease Mitigation, Control and Export Support (DMCES) and Veterinary Research Unit (VRU), both part of Defra's Food and Farming Group), Veterinary Laboratories Agency, Health Protection Agency, University of Birmingham and Heartlands Hospital, Birmingham, Department of Health, Chemicals Regulation Directorate, The Food and Environment Research Agency, Food Standards Agency, Scottish Government, Health Protection Scotland, Scottish Agricultural College, Office of the Chief Veterinary Officer, Welsh Assembly Government, University Hospital of Wales, Cardiff, Agri-Food and Biosciences Institute, the Biotechnology and Biological Sciences Research Council and the Centre for Environment, Fisheries and Aquaculture Science (CEFAS).

The MRSA sub-group of DARC has a wider membership that includes many of the above institutions but also members of academia, the veterinary profession and farming industry and a charity that works primarily on AMR issues affecting pet animals. Many of these individuals have international networks of contacts of great value to Defra in progressing AMR understanding and issues. Some universities involved in the sub-group have also successfully bid for AMR R&D funding, but this is allocated by tender and not as a consequence of their collaborative work with Defra.

VMD also has a wide network of contacts throughout the veterinary pharmaceutical industry, regulatory authorities and internationally on the full range of activities in which it is involved. It also liaises closely in the UK with the independent multi-sectoral professional group, the Responsible Use of Medicines in Agriculture Alliance (RUMA).

4.3 Use and value of advisory bodies and external specialist advisers

Veterinary medicines

Advice for the research requirements documents (RRD) for the Veterinary Medicines research programme is sought from the VMD Research Programme Steering Group, colleagues in Defra and other government departments, agencies and outside bodies. The independent expert Veterinary Products Committee (VPC) and the Veterinary Residues Committee (VRC) and their sub-committees may also be asked to advise on the research particularly its quality, relevance and implications during and after completion of projects.

The VPC is an independent advisory committee with expertise to recommend on the authorisation of veterinary medicines. Membership covers a wide range of disciplines including pharmacology, toxicology, veterinary, medical, etc. When necessary the committee will identify topics for further research to assist the VMD in the development of policy. The VRC is another independent advisory committee with expertise to consider the significance of residues of veterinary medicines in food. Membership covers a wide range of disciplines including residue chemistry, pharmacology, toxicology, veterinary, consumer and retail interests.

Concept notes and full research proposals received in response to the RRD will be peer

reviewed by external independent advisors and the VMD for the potential to contribute to the policy needs.

The VMD R&D Research Programme Steering Group will consider the implications for policy of the results from completed individual studies.

A review of the programme will be held every 3-5 years. Independent external advisors will assess all projects, give their opinions on the relevance of the current research programme to Defra's current policy needs and provide recommendations for future research. Defra personnel and representatives of other Government Departments and Agencies (as appropriate) will consider the contribution that the programme has made to the implementation of policy.

Antimicrobial resistance

Key specialists include staff at the University of Birmingham/ Central England PCT, DH, HPA MRSA Reference laboratory, Scottish MRSA Reference laboratory, University of Liverpool, Royal Veterinary College, Pig Veterinary Society, National Pig Association, and the VLA.

Formal committees /advisory bodies where Defra (including VMD) supply secretariat (as well as members and expertise) include DARC, the DARC MRSA sub-group, the joint ARHAI (Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections) / DARC (Defra Antimicrobial Resistance Coordination Group) Extended Spectrum Beta-Lactamases (ESBLs- an important type of AMR in public and veterinary health) sub-group, ACDP (Advisory Committee on Dangerous Pathogens) and UKZADI (UK Zoonoses, Animal Diseases and Infections Group).

Through our contacts network we can also convene small ad hoc groups for specific purposes over a limited period. For example we are currently setting up a DARC sub group to discuss prescribing practices with veterinary practitioners. We also regularly provide briefing for and contribute to discussions on the Defra consumer panel, and get feedback from them.

These bodies supply us with:

- A wide range of expert opinion beyond what is available within the team or department;
- An insight into the thinking and drivers of Other Government Departments, consumers and industry sectors, so that our policy is joined up and we can anticipate the reaction of industry to policy initiatives and consultation exercises; and
- Allow us to demonstrate to industry that policy is evidence based and that we value their input to legislative and policy development.

Most of the deep specialists we use come from within government (usually VLA and HPA in our case) on either a contractual or a personal / informal basis (the usefulness (and cost saving) of contacts made through sitting on intergovernmental groups cannot be underestimated in this respect). Open tender research contracts expand the net of expertise available to a wider academic pool.

5. MEETING NEW EVIDENCE NEEDS

5.1 Overall approach to meeting your evidence needs

The VMD and Defra (with respect to antimicrobial resistance issues) will continue to work as outlined in the sections above to identify the need for evidence in work areas using a network of internal and external advisors. The priority for work to provide the necessary evidence by either research or non-research means will be kept under continuous review throughout the year. Where necessary and appropriate action will be taken during the year or as part of an integrated annual plan. All proposals for evidence-gathering work will be assessed on:

a) the relevance, urgency and quality of the science
b) the likelihood of success of the work
c) the skill and experience of the contractors and collaborators and
d) whether the costs are appropriate.

Only proposals which pass independent peer review (see 4.3 above) satisfying all these criteria and follow Defra procedures for science/evidence procurement will be considered for funding.

Projects will be monitored through submission of annual/final reports to ensure that all milestones are met, and that the project objectives are achieved. Whenever possible, initial implementation meetings will be held with contractors at the start of a study. This will be followed by monitoring meetings at least once per year and more frequent discussions to review the progress of the work and resolve any problems that may have occurred in the course of the work. Changes to the agreed research plan or project objectives will only be permitted after the commissioning team has considered a written application setting out why such changes are warranted.

Project final reports will be peer reviewed under the following terms of reference:

1: To consider whether the scientific approaches were appropriate for the aims and objectives of the project and if they were taken forward competently.

2: To consider the extent to which the output of the project meets the aims and objectives and whether the conclusions are based on sound evidence.

3: To assess the effectiveness with which appropriate opportunities for technology transfer were addressed and, in particular, whether reports and publications were delivered to an appropriate standard.

4: To consider the collaboration with other institutes and universities.

5: To advise on what form any continuation of the work should take.

The VMD R&D Research Programme Steering Group and the Defra Antimicrobial Resistance Co-ordination group, the VPC (and its sub-committees where relevant) and

the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (an independent advisory committee to the Department of Health) will be asked to consider the implications for policy of the results from completed individual studies.

As discussed in 4.3 above, a review of the programme will be held every 3-5 years using independent external advisors to assess all projects and give their opinions on the relevance of the current research programme to Defra's current policy needs and provide recommendations for future research.

5.2 Evidence investment forecast

Annex 1

Key references supporting the current state of knowledge [Return to Section 2.1]

The Path of Least Resistance. 1998. Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance, Department of Health.

Overview of Antimicrobial Usage and Bacterial Reistance in Selected Humans and Animal Pathogens in the UK: 2007, published 2010.

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House of Lords Select Committee on Science and Technology. Session 1997-98, 7th Report. Resistance to Antibiotics and Other Antimicrobial Agents. Chairman Lord Soulsby. London: The Stationery Office.

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Partnership, Priorities and Professionalism: A Strategy for Enhancing Veterinary Surveillance in the UK. 2003. Department for Environment, Food and Rural Affairs.

Outline of an Animal Health and Welfare Strategy for Great Britain. 2003. Department for Environment Food and Rural Affairs, Scottish Executive and Welsh Assembly Government.

Success and outputs from Defra's Surveillance Strategy 2008

Franklin A *et al*. Antimicrobial Resistance: Harmonisation of national antimicrobial monitoring and surveillance programmes in animals and in animal derived food 2001. In Antimicrobial Resistance: Reports prepared by the OIE ad hoc Group of Experts in Antimicrobial Resistance. OIE Technical review, Vol 20, Pp 859-870

Defra Antimicrobial Resistance in Animals Policy Statement: Aug 2009

Sales of antimicrobial products authorised for use as veterinary medicines, antiprotozoals, antifungals and coccidiostats in the UK in 2008.

Overview of Antimicrobial Usage and Bacterial Resistance in Selected Human and Animal pathogens in the UK: 2004

DARC 09/25 Strategy for developing and implementing a programme of surveillance for antimicrobial resistance in animals in England and Wales
(revised December 2008)

Better surveillance needed to fight spread of antimicrobial resistance in zoonotic infections: EFSA 2009-12-14

Proposed Draft Guidelines for Risk Analysis of Food borne Antimicrobial Resistance (N01-2008, N02- 2008, N03-2008): CODEX

Draft report of the ESBLs sub-group of DARC and ARHAI

Scientific Opinion of the European Centre for Disease Prevention and Control; Scientific Opinion of the Panel on Biological Hazards; Opinion of the Committee for Medicinal Products for Veterinary Use; Scientific Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks: Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections 2009

CODEX Reflection paper on MRSA in food-producing and companion animals in the European Union: epidemiology and control options for human and animal health:

CVMP strategy on antimicrobials 2006-2010 and status report on activities on antimicrobials (EMEA/CVMP/353297/2005):

Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008

Directive 2001/82/EC as amended by 2004/28/EC,

Mandate, objectives and rules of procedure for CVMP scientific advisory group on antimicrobials (SAGAM) ref: EMEA/CVMP/SAGAM/241147/2006

HPA: Investigations into multi-drug resistant ESBL-producing Escherichia coli strains causing Infections in England. September 2005. 2006. London, Health Protection Agency.

Potz NA, Hope R, Warner M, Johnson AP, Livermore DM. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. J Antimicrob Chemother 2006;58: 320-6.

Report on Microbial Antibiotic Resistance in Relation to Food Safety. 1999. Advisory Committee on the Microbiological Safety of Food.

Report on Microbial Antibiotic Resistance in Relation to Food Safety: Recommendations and Government's Response. 1999. Advisory Committee on the Microbiological Safety of Food.

The Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann) Report (1969)

Scientific Document: The Community Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union in 2004-2007
www.efsa.europa.eu/en/scdocs/scdoc/1309.htm

Annex 2

Glossary

AFBI	Agri-Food and Biosciences Institute (of Northern Ireland)
Antibiotic	A substance produced by or derived from a micro-organism, which selectively destroys or inhibits the growth of other micro-organisms
Antimicrobial	A compound which at low concentrations exerts an action against micro-organisms and exhibits selective toxicity towards them. The term includes any substance of natural, synthetic or semi-synthetic origin that is used to kill, or inhibit the growth of, micro-organisms. Antimicrobials include antibiotics, disinfectants, preservatives and other substances
Antimicrobial resistance (AMR)	The ability of a micro-organism to grow or survive in the presence of an antimicrobial that is usually sufficient to inhibit or kill micro-organisms of the same species
ARHAI	Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections (ARHAI). Established in April 2007 to provide practical and scientific advice to the Government on strategies to minimise the incidence of healthcare associated infections (HCAI) and to maintain the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in humans and animals
ARMRL	Antibiotic Resistance Monitoring and Reference Laboratory is the national reference laboratory responsible for the detection and investigation of antibiotic resistance in medical isolates
Bacteria	A large group of single-celled, prokaryote (cells that lack membrane-bound nuclei) micro-organisms
β-Lactam	Semi-synthetic antibiotics derived from penicillin G or cephalosporin C, natural antibiotics produced by the mould *Cephalosporium acremonium*
β-Lactamase enzymes	Enzymes produced by some bacteria and that are responsible for their resistance to beta (β) -lactam antibiotics
BSAC	British Society of Antimicrobial Chemotherapy

CEFAS	Centre for Environment, Fisheries and Aquaculture Science
Commensal	Living together of one population (or individual) with another where neither is benefited nor harmed
CVMP	Committee for Medicinal Products for Veterinary Use, European Medicines Agency
DARC	The Department for Environment, Food and Rural Affairs (Defra) Antimicrobial Resistance Coordination Group
DARDNI	The Department of Agriculture and Rural Development, Northern Ireland
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
Disinfectant	An agent that destroys, neutralizes or inhibits the growth of disease-carrying micro-organisms
DMCES	Disease Mitigation, Control and Export Support, part of the Veterinary Science Team (VST) of Defra's Food and Farming Group
EARSS	EARSS is an international network of national surveillance systems and monitors resistance in a number of bacterial isolates. More than 750 laboratories from 28 countries participate in the EARSS programme
EFSA	European Food Safety Authority
EMA (was EMEA)	European Medicines Agency. The central EU regulatory agency for the evaluation of medicines developed by pharmaceutical companies for use in the EU
ESBL	Extended-Spectrum Beta (β) -Lactamases (ESBLs) are enzymes that can be produced by bacteria making them resistant to penicillins and cephalosporins
FERA	Food and Environment Research Agency - an executive agency of Defra
FFG	Food and Farming Group, part of Defra
Food animals	Animals reared for food including cattle, sheep, pigs,

	poultry, salmon and trout. Bees are also included as a food animal because they produce honey
HPA	Health Protection Agency
MDR	Multi-drug resistant micro-organism
MRSA	Meticillin resistant *Staphylococcus aureus*: a species of bacteria that has developed resistance to the antimicrobial meticillin (and other related antimicrobials) and is primarily of significance to public health although it can also be carried by and sometimes can affect animals too
Non food animals	Animals not reared for food. These are mainly companion animals including, dogs, cats, horses, birds and small mammals (e.g. rabbits)
RUMA	RUMA (the Responsible Use of Medicines in Agriculture Alliance
SAC	Scottish Agricultural Colleges
SRO	Senior Responsible Officer for a particular programme of work within Defra
Therapeutic product	A product which treats or prevents disease
UKZADI	UK Zoonoses, Animal Diseases and Infections Group
Virus	A virus (from the Latin virus meaning toxin or poison) is a small infectious agent that can replicate only inside the cells of other organisms
VLA	Veterinary Laboratories Agency - an executive agency of Defra
VMD	Veterinary Medicines Directorate - an executive agency of Defra
VPC	Veterinary Products Committee, an independent advisory committee with expertise to recommend on the authorisation of veterinary medicines. Membership covers a wide range of disciplines including pharmacology, toxicology, veterinary, medical etc. When necessary the committee will identify topics for further research to assist the VMD in the development of policy.

VRC	Veterinary Residues Committee, an independent advisory committee with expertise to consider the significance of residues of veterinary medicines in food. Membership covers a wide range of disciplines including residue chemistry, pharmacology, toxicology, veterinary, consumer and retail interests.
VRU	Veterinary Research Unit, part of the Veterinary Science Team (VST) in Defra's Food and Farming Group
VST	Veterinary Science Team (VST), part of Defra's Food and Farming Group

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