



ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES

Ms C O'Driscoll
Canine Health Concern

BY EMAIL

30 July 2010

Dear Ms O'Driscoll,

Thank you for your letter of 29 June and the papers sent with it. I have noted that you do not indicate that this letter is an open communication unlike your previous letter. In the interests of transparency, I would like to maintain the principle that this debate is exchanged in public view and so may I ask if you have any objections to your documents being placed on the VMD website along with the VMD's response? It would be helpful to have a response as soon as possible but in any case, if I do not hear to the contrary before the end of business on 31 August 2010 we will proceed on the presumption you agree and put the documents on our website.

Critically reviewing Canine Health Concern's (CHC) letter, attached papers and references totalling over 380 pages will take some considerable time and, therefore, this response may be supplemented by further comment or questions in due course. It is clear that the contents are largely opinion based upon a considerable amount of anecdotal comment from dog owners, various third party opinions and quotes (some adequately referenced and some not) and, at least in those areas where VMD is directly involved, the information provided is often selective, misinterpreted, misunderstood or quoted out of context. The principle thrust of CHC's response appears to be challenging the safety of canine and feline vaccines both in terms of their authorisation and their use by the veterinary profession in the UK. The over-riding impression is of a CHC position based on an eclectic mix of published 'extracts', utilising poor scientific rigour and anecdotes to justify an anti-vaccination stance. As a science-based regulatory agency such poorly substantiated, selective arguments rarely gain much credence although we will try to extract the relevant points you make and address them.

Unfortunately, the confusing array of material in the CHC papers collectively serves to distract the public from the important benefits of vaccination as set out in the WSAVA guidance which is disappointing. The WSAVA guidance has encapsulated their fundamental concept as: ***We should aim to vaccinate every animal with core vaccines, and to vaccinate each individual less frequently by only giving non-core vaccines that are necessary for that animal.*** Can you confirm if CHC agrees with this principle for if we are to discuss using the WSAVA guidance as the template for national UK vaccination programmes we must surely agree on the basic tenet of that guidance?

On the plus side it is rewarding to note that CHC appears to have moved from its position of being entirely against vaccination to one that perhaps supports the WSAVA line. However, your website still adopts a challenge to the benefit of vaccination utilising unreferenced adverse comments under your 'pet vaccines myths' section. Conducting our exchanges in the public domain will at least allow the pet owner to reach their own conclusions in deciding when to vaccinate their pet animal. The overwhelming weight of scientific evidence is that the benefit of vaccination against the common, life threatening viral diseases in cats and dogs far outweighs any risks associated with the use of a vaccine. There are recognised risks to vaccination and those that do exist are well documented but are small compared to the risks of the overt infectious diseases they are designed to prevent. Adverse reactions are clearly set out on the labelling of the vaccines.

In developing CHC's arguments you raise questions about the independence of the Veterinary Medicines Directorate, the government agency charged with authorising veterinary medicinal products for the UK market. From the outset, I would like to strongly refute any allegation that the VMD is concerned with supporting the financial interests of pharmaceutical companies. The VMD has an extremely high reputation within the EU for its independence, integrity and quality of its science based regulation of veterinary medicines. The VMD is a Defra Agency and its staff are Civil Servants who work to the Civil Service Code. They also care passionately about their contribution to society and many of them own pet animals too. In the relatively small field of veterinary science it is almost inevitable that some VMD employees will have had previous experience working directly or indirectly for the pharmaceutical industry. However, to focus on this as entirely negative is disingenuous. To use my own Curriculum Vitae as an example, my experience in the pharmaceutical industry commenced in the clinical development of medicines, then in a veterinary advisory/educational role predominantly for farmers and ended in a business leadership role. Prior to this I worked in a mixed veterinary practice and taught veterinary science at the Royal Veterinary College, London. Privately, I have a strong interest in pedigree dogs (as you have suggested through highlighting my unpaid role at the Kennel Club). May I suggest, using this abbreviated summary of my own CV as an example, that a breadth of experience from general practice, veterinary education, commercial development and technical support for veterinary medicines and business management, is an effective base for leading a regulatory agency. Many of my colleagues have a similar employment history and are excellent in their role. However, as the issue of commercial interest of regulatory staff appears to be an important part of the CHC argument let me state I have no financial interest in any veterinary pharmaceutical company and no potential conflict of interest exists and has not done so for more than 13 years. This is true for nearly all the VMD's employees and where any potential conflict of interest does exist, usually because of recent previous industry employment, this is openly declared and individuals are not permitted to work on applications where their interest could affect their opinion.

It is important for the public to also know that decisions on the authorisation of individual vaccines are based on scientific data submitted in accordance with EU legislative requirements and guidelines. National regulatory work is increasingly scrutinised by scientists from across the EU and, in addition, in the UK the Veterinary Products Committee (VPC) reviews the quality of work of the VMD and ensures decisions are based on established and recognised science. The VPC is made up of scientists from the research and academic community and any commercial interests they may have are declared and their input restricted accordingly. The VPC has produced its own independent report on Feline and Canine Vaccination and we would again refer you to the findings published on their website <http://www.vmd.gov.uk/vpc/Working/feline.html>.

Our work is funded by fees from the pharmaceutical industry. The Government requires the VMD to charge for its services as it would be unreasonable to expect the public purse to fund the work of the agency in authorising veterinary medicines. The same principle applies to the authorisation of human medicines. It is reasonable to expect those companies who will derive a commercial benefit from the regulatory system, when product specific marketing authorisations are granted, to pay for the assessment processes that lead to it. However, this does not affect our assessment decisions as they are driven by scientific assessment, not profit (we are charged by Government to achieve cost recovery), and fees for assessing applications and for ongoing regulation of authorised veterinary medicines are not dependant on a positive outcome for the industry. The work of the VMD, including our annual accounts, is reported on the VMD website (www.vmd.gov.uk). I, therefore, object strongly to your

suggestion that industry funding might compromise the VMD's independence – it does not.

The VMD Position Paper on Authorised Vaccination Schedules for Dogs <http://www.vmd.gov.uk> sets out the regulatory framework for veterinary vaccines in the UK (which reflects the regulatory requirements across the EU). In providing a comprehensive and balanced analysis of the safety and efficacy of canine and feline vaccines it provides details of the process that has led to authorised vaccination schedules for individual products marketed in the UK. We would restate our position that the majority of authorised vaccination schedules for dog vaccines in the UK are in general accord with the WSAVA Guidelines and have attached the VMD Position Paper in Annex 1 in the hope that it will be re-read in conjunction with the latest published WSAVA Guidelines <http://www.wsava.org/VGG1.htm>. It is also worth reviewing the Pictorial Fact Sheets on the WSAVA website as a reminder of the severity of clinical signs of these life-threatening diseases in unvaccinated animals. A quote from CHC's own website confirms this at least for one core disease: "Distemper kills only half of affected dogs...." although the inclusion of the word 'only' is surprising.

In considering vaccination, it is important to maintain a clear distinction between the frequency of vaccination for core-Modified Live Viral (MLV) vaccines and other live and killed, non-core vaccines (both viral and bacterial) that are administered to dogs. In our view CHC's opinions and statements fail to maintain this distinction and this is regrettable as it has the potential to mislead the casual but concerned reader on the need for vaccination and the advisability of annual re-vaccination for specific non-core vaccines. It is VMD's understanding that re-vaccination intervals of 3-4 years for core MLV components are routinely practised by most veterinary surgeons in the UK but ultimately it is for the veterinary surgeon, in consultation with the owner, to determine the frequency of vaccination for the agreed disease components, taking account of the health of the animal and the risk of exposure to infection. I am not aware of any data that refutes this assertion.

The authorised duration and onset of immunity of all UK authorised dog vaccines is attached in Annex 2 as background information for pet owners and veterinary surgeons. It must be stressed that there is no legislative compulsion to vaccinate pet animals other than for animals travelling abroad where rabies vaccination is mandatory under the Pet Travel Scheme (PETS) if the pet is to return to the UK. However, the VMD would support the view that vaccination of cats and dogs is advisable and in this we agree with the fundamental WSAVA concept.

Inactivated (killed) leptospira and 'Kennel Cough' vaccines (live and inactivated) are administered more frequently than the core-antigens, usually annually, to maintain protective levels of immunity. Therefore, a routine annual visit to a veterinary surgeon may often be required if there is a desire to keep all recommended vaccinations up to date. The failure to adequately distinguish between the duration of immunity of core-MLV and non-core vaccines in your paper is misleading to those less informed on the subject. There is, therefore, no reason, from VMD's perspective, why an "annual visit to the vets" for booster vaccinations should result in the administration of unnecessary core-antigens. Many pharmaceutical companies have developed extensive ranges of vaccine products that enable a veterinary surgeon to tailor the vaccination schedules appropriately for the animals under their care. Targeted protocols reduce the risk of unnecessary vaccination whilst ensuring adequate levels of protection.

The authorised duration and onset of immunity of all UK authorised dog vaccines is attached in Annex 2 as background information for pet owners and veterinary surgeons.

CHC's recent article (Dogs Today, June 2010) and the content of the CHC website suggesting homoeopathic nosodes as an alternative to authorised vaccines is, in our view, irresponsible given the absence of any proven efficacy and the potential serious safety risks posed by such products in terms of the unknown quality of the biological starting materials and unproven efficacy. Unlike authorised vaccines, nosodes have not been manufactured in approved facilities that operate to EU standards of Good Manufacturing Practice (GMP), have not been independently evaluated for their benefits versus risks and there are no obligations on manufacturers to monitor and report adverse events. Given your concern about the safety of vaccines, it is surprising to see CHC support nosode use given the lack of suitable independent scientific assurance on safety and efficacy.

Serological testing may be used to monitor immunity following immunisation with core-vaccines and, depending on the results, has the potential to reduce the frequency of re-vaccination. There is no regulatory barrier to serology being used for this purpose. The use of antibody titres as a correlate of protection is reviewed in the VMD Position Paper and we would re-emphasise the need for caution when interpreting results from various serological assays where standardisation is not assured. A serological titre correlated with protection oversimplifies the science of immunology and does not guarantee an individual animal will be protected from infection due to the complexity and involvement of other immunological parameters. The risks of over-vaccination are considered extremely small compared to the risk of exposing unprotected animals to life-threatening infection. Nevertheless, the regulatory framework does not preclude the possibility of using serological tests to help determine re-vaccination schedules and we would suggest that owners discuss such an approach with their veterinary surgeon as this is surely an individual choice and should not be needlessly imposed by regulation.

The VMD Position Paper on Authorised Vaccination Schedules for Dogs addresses most of the other points in your recent correspondence and we do not intend to repeat what is already available on our website. However, we do provide the following comments on new issues and attempt to clarify some areas of misunderstanding relating to the wording of authorised vaccination schedules:

Comparison of WSAVA Guidelines recommendations (A) against UK authorised vaccination schedules (B).

1. Puppy vaccination protocols.

A. WSAVA 2010 Guidelines recommended typical schedule for puppies and first booster for core-vaccines:

- 1st vaccination 8-9 weeks of age
- 2nd vaccination 12-13 weeks of age
- 3rd vaccination 14-16 weeks of age
- 12 month booster for all dogs.

The recommended vaccination schedule is designed to allow for high levels of Maternally Derived Immunity (MDA) in puppies whilst ensuring that pups with poor levels are protected at an early age. The WSAVA Guidelines define the primary vaccination of 3 doses and 12 month booster as the “basic immunisation protocol”.

This results in:

Total number of core vaccine administrations in first year = 4.

B. Authorised core-vaccination schedule for puppies for one representative dog vaccine authorised by VMD:

- 1st vaccination to pups 6 weeks of age and over
- 2nd vaccination 3-4 weeks later, but not before 10 weeks of age
- No requirement for 12 month booster.

This results in:

Total number of core vaccinations in first year = 2.

2. Re-vaccination of adult dogs.

A. WSAVA Guidelines maximum recommended schedule for re-vaccination of adult dogs:

- Re-vaccination at intervals of 3 years or longer (not more often than every 3 years), unless special conditions apply
- The re-vaccination schedules do not generally apply to killed core vaccines nor to the optional vaccines and, particularly, not to vaccines containing bacterial antigens (such as Leptospira or Bordetella vaccines). These schedules are often annually applied.

This results in:

Total number of vaccinations with core-MLV vaccines from year one to 11.5 years of age (estimated median lifespan of average pedigree dog) = 3.

B. Authorised vaccination schedule. The recommended schedule for revaccination of adult dogs for one representative dog vaccine:

- Duration of immunity is three years for distemper (CDV), adenovirus (CAV1 and CAV2) and parvovirus (CPV).
- It is recommended that dogs be re-vaccinated with CDV, CAV and CPV every three years.

This results in:

Total number of vaccinations with core-vaccines from year one to 11.5 years of age (estimated lifespan of average dog) = 2.

3. Lifetime core-vaccination of dogs.

- A. Total number of core-vaccinations according to WSAVA Guidelines over 11.5 year period to a puppy and subsequently throughout its adult life = 7 (maximum) or 4 (assuming lifetime protection of MLV components).
- B. Total number of core-vaccinations according to a representative UK authorised vaccination schedule over a 11.5 year period to a puppy and subsequently throughout its adult life = 4.

In conclusion, based on the representative vaccination schedule of an authorised vaccine in the UK, there is no legitimacy in CHC's accusation that the regulatory process in the UK encourages the over-vaccination of dogs. Administration of vaccines to dogs in accordance with the approved schedules should not result in the administration of more core-vaccinations than recommended by the WSAVA Guidelines over the lifetime of a dog and in some cases may result in less vaccination.

4. Authorised vaccination schedules. Duration of immunity and re-vaccination schedules.

The duration of immunity for an authorised vaccine is established by the submission of scientific data to demonstrate that an animal will be protected against infection at the longest period claimed by the manufacturer i.e. a four year duration of immunity claim would require a four year animal study. The final wording on the authorised product literature is an accurate description of the scientific studies performed to support the claims for that particular product. It would not be justified or appropriate to extrapolate beyond this period without additional data specific to each formulated vaccine. An assumption that all vaccines would have the same level of efficacy is not justified. It is, however, for a veterinary surgeon to take account of other factors and publications, including the WSAVA Guidelines and local disease epidemiology, when advising on the appropriate, optimum, vaccination protocol for their client's pet.

A recommended booster interval of, for example "up to 4 years", as worded on an authorised SPC, is not intended to encourage more frequent vaccination intervals unless justified by the specific requirements of the vaccinated animal (e.g. outbreak of disease locally). We understand the majority of veterinary surgeons administer vaccines no more frequently than the claimed duration of immunity, unless there are justified health, epidemiological or other risk factors that support a revised schedule. This is a point recognised in the WSAVA guidance. It is, therefore, difficult to comprehend CHC's claims that annual vaccination is the norm unless you are referring to the appropriate annual vaccinations recommended for non-core vaccines? Alternatively can you provide evidence that annual MLV re-vaccination schedules are used extensively?

It is therefore our view that annual vaccination of MLV components is not the "norm" and the extended duration of immunity offered by several canine vaccines is evidence of the progress made in this area in the last 10 years. The VMD has a good record on this issue and has been the leading EU agency for authorising 3-4 year re-vaccination intervals for the majority of dog vaccines.

5. Vaccine safety is not assured at the point of authorisation?

Medicinal treatment is not risk free thus justifying the need for a regulatory system to provide assurance on the expected efficacy of the therapy and, more importantly, information on the specific safety issues associated with any medicinal treatment. Regulation, therefore, seeks to balance the risks against the benefits of treatment and achieve a positive outcome. As the immunological system of each individual is specific and has individual capacity for variance, vaccine usage is placed under veterinary control so that the decision to vaccinate can be made by the client taking expert veterinary advice tailored to the animal patient. It is recognised that individual animals (and humans) may react differently to 'the norm' when being treated with a medicine (including a vaccine) so assuring safety for each individual animal is an unreasonable expectation. Nevertheless, the overwhelming majority of cat and dog vaccinations are not associated with any adverse effects. CHC's own evidence appears to support this view as CHC quote 'hundreds of cases' of suspected adverse reactions which in the face of millions of doses used per annum is suggestive of a low incidence of problems.

The controls on prescribing, supply and use are put in place to ensure that the risk of vaccination is transparent and kept to a minimum. The pre-authorisation safety tests conducted on MLV vaccines are laid down in European Pharmacopoeia monographs and Guidelines. The studies are designed to identify any common local and systemic reactions to a treatment and, for live vaccines, the potential of vaccine organisms to revert to virulence or spread within and between animals and to humans. There are inevitably limitations for laboratory studies to demonstrate all the risks associated with a treatment and, in particular, the difficulty in identifying safety issues that are multi-factorial (e.g. genetic predisposition and physiological/immunological variation between species, breeds or familial groups). Thus field studies (clinical trials) in a range of breeds follow on from the laboratory studies and are conducted across different husbandry systems and in various locations. They are performed before any vaccine is authorised to provide additional assurance on the safety profile of the product. Even given this amount of data the assurance on product safety has limitations and, therefore, post-authorisation surveillance systems monitor reported adverse reactions (in the UK this is the Suspected Adverse Reactions Surveillance Scheme (SARSS)). This pharmacovigilance system is constructed on the principal of trend analysis which takes account of the likelihood of under-reporting and to some extent caters for the paucity of information available on the current epidemiology of diseases, especially in companion animals. Individual reports in isolation are of little value but when they are considered collectively useful information is frequently revealed. The VMD Position Paper published information on the most frequently reported adverse events between 2005 and 2010. Information is provided transparently and the VMD routinely publishes information on suspected adverse reactions reported to its SARSS team. Having checked, we cannot identify reports in our database on the dogs you claim suffered from adverse reactions whilst owned by you. Can I stress that the SARSS is not limited to reporting from veterinary surgeons (and never has been) and animal owners can complete a report and submit it. I strongly urge you and those who have joined with you in attempting to raise public alarm related to vaccine use to report the suspected adverse reactions you experience to the SARSS. A report form is available on the VMD website. In the interests of the animals you wish to protect, each and every one of the hundreds of people who are supporters of CHC should consider completing a report of the suspected adverse reactions their pets have experienced. To those who already have done so we give our thanks for their help and co-operation.

6. Retrovirus contamination of dog and cat vaccines.

Biological and immunological knowledge continues to develop as science progresses. Scientific knowledge is not absolute and increasingly sensitive and sophisticated techniques continue to expand the knowledge base. Thus what was historically considered acceptable changes over time. In April 2010, the VMD and other regulatory agencies were made aware of the publication of a peer reviewed article which presented new information regarding the detection of feline replication-competent endogenous retrovirus RD114 in some live attenuated vaccines commercially available in the EU and Japan (Miyazawa T et.al, Isolation of an infectious endogenous retrovirus in a proportion of live

attenuated vaccines for pets. J.Virol, 2010, Apr;84(7):3690-4). The research groups used novel, highly sensitive methods of detection based on new molecular technologies to identify the presence of minute quantities of virus in cell cultures used for vaccine production.

In the light of this new information, the Executive Director of the European Medicines Agency (EMA) referred the issue to the Committee for Veterinary Medicinal Products (CVMP) to give a scientific opinion on the issues raised by these findings. The Committee is currently considering the potential risks to both cats and dogs. We will monitor developments on this issue and take any necessary regulatory action recommended by the CVMP to safeguard the health of vaccinated animals. At this stage, however, the benefits of vaccination are considered to outweigh the potential risks given the proven safety record of both canine and feline vaccines on the UK market.

Yours sincerely



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ANNEX 1. VMD POSITION PAPER ON AUTHORISED VACCINATION SCHEDULES FOR DOGS

INTRODUCTION

Louis Pasteur in the 19th century demonstrated the ability to protect chickens against fowl cholera (*Pasteurella multocida*) (Fenner *et al*, 1997) and thus demonstrated the benefit of vaccination in animals and paved the way for the development of the array of veterinary vaccines we have today.

Since Pasteur's work, vaccination against infectious disease has been used successfully to protect animals from many serious diseases some of which were also significant risks to humans. Veterinary vaccine development has paralleled the research and development of vaccines in the human field. However, in veterinary medicine there is a much wider range of products reflecting the diversity of animal species and the plethora of diseases that may commonly affect companion and food producing animals. As a consequence the incidence of many common, life threatening and debilitating diseases is now low and the development of safe and effective veterinary vaccines can be said to have been a major success story for improvement in animal health and welfare.

However, success in disease control is often followed by new challenges. In pet animals, and particularly for dogs and cats, diseases that were once chronic scourges have now become relatively rare in developed countries like the UK. As the public memory of the consequences of these diseases fades so the rationale for routine vaccine programmes is increasingly questioned. A healthy debate of the pros and cons of vaccination is valuable as it is entirely possible that a disease can become so rare that risks associated with vaccination can outweigh the risk of contracting the illness. However, such events are rare and likely to remain so as world-wide travel of people and their pets increases. The gold standard is provided by the example of small pox in humans. The last case in man was recorded in 1977 and in 1980 the WHO officially announced smallpox had been eradicated from the world. The current low incidence of dog and cat infectious diseases provides an incentive for some animal owners to argue vaccination is no longer necessary. This is generally regarded as being impractical and so the debate has focused upon the frequency of vaccination required to provide protection throughout the animal's lifetime and the potential for routine vaccination to do harm to the individual animal. Advising on the correct vaccination course to follow is not an easy task as a routine programme of vaccination may require adaption to the local epidemiology of the various diseases to provide the best health security. It is right therefore, that the decision is taken by the animal owner following discussion and advice from their veterinary surgeon.

Before a veterinary vaccine can be placed on the UK market it undergoes a rigorous independent scientific assessment to ensure the product meets the required standards. In the UK the standards are set by the European legislation. Independent assessment seeks to ensure three major factors are in place before any vaccine is made available for use:

- vaccines are manufactured to a consistent and acceptable quality using high grade materials and are uncontaminated with potentially harmful infectious agents or other toxic substances;
- vaccines are safe to be administered to young and older animals where relevant, and pose no risk to the owner, their families or other animals and persons coming in contact with vaccinated animals. Where necessary, specific warnings are added to the product literature to minimise any risk of an adverse reaction following administration of the product;
- high quality scientific data is available to support the primary and any re-vaccination (booster) schedule and this has been assessed to ensure the vaccine can be expected to provide the required onset and duration of immunity claimed by the manufacturer to protect animals against disease.

In the case of dogs and cats, vaccines are manufactured and marketed for the globally important viral and bacterial infectious diseases and for diseases that are a risk for particular populations exposed to diseases with geographically limited circulation.

The World Small Animal Veterinary Association (WSAVA) has produced guidelines (Day *et al* 2007) which divide canine and feline vaccines into core and non-core vaccines. Core vaccines are defined as those that protect animals from severe life-threatening diseases caused by viruses that have a global distribution (i.e. for dogs these are canine distemper virus (CDV), canine adenovirus (CAV) and canine parvovirus (CPV)). Non-core vaccines are vaccines for animals whose geographical location, local environment or lifestyle places them at risk of contracting other specific infections. The WSAVA Guidelines also classify some vaccines as not recommended where they believe there is insufficient scientific evidence to justify their use. However they may still be used where the diseases they intend to immunise against have a particular clinical significance.

There are approximately 320 veterinary vaccines or immunological products currently holding Marketing Authorisations in the UK for companion animals, horses and the major food producing animals. At the time of writing, 61 are authorised for use in dogs in the UK and 35 products are authorised for cats. The majority of these are multivalent vaccines containing a number of antigens to protect against a range of important diseases. Details of the products authorised for dogs are provided in Annex 1. The maximum Duration of Immunity (DOI) for some of the core vaccines has been justified as four years with a range for all vaccines extending between 1-4 years. For the majority of vaccines in the UK their recommended use closely parallels the WSAVA Guideline recommendations.

Annex 1 has been constructed to provide a summary of the currently authorised primary vaccination and revaccination periods for core, non-core and other vaccines for dogs. As this information may change as companies vary their authorisations it is important to refer to the latest version of the SPC for a product which can be viewed in the VMD's Product Information Database:

<http://www.vmd.gov.uk/ProductInformationDatabase/>

The focus for this document will be the canine vaccines.

CANINE DISTEMPER, PARVOVIRUS AND ADENOVIRUS (DISEASES TARGETED BY CORE-VACCINATION)

1. Canine Distemper Virus (CDV)

1.1 Canine distemper is a highly contagious and particularly severe viral infection of dogs and other carnivores including foxes and ferrets. The fox acts as a potential wildlife reservoir of infection. The disease has been recognised for at least two centuries whilst the first modified live canine distemper vaccines were not developed until the 1940s. All the current UK products are live attenuated vaccines. A recognised problem with the development of the first vaccines was post-vaccinal encephalitis causing neurological symptoms. These adverse reactions were seen especially from vaccine strains propagated in canine cell cultures (Carmichael, 1997) and were resolved by manufacturing the vaccines using alternative strains on less reactive cell lines. This form of adverse reaction is extremely rare with modern CDV vaccines (Appel, 1999). Despite being safe for use in dogs, some vaccine strains can remain virulent when used to immunise other species and care must be exercised when using live attenuated vaccines in ferrets, for example. As a modern disease, Canine Distemper usually occurs in younger dogs and although older animals can be affected, the chronic and classic forms (e.g. hardpad) of the diseases are extremely rare.

1.2 The virus is unstable in the environment (compare with Canine Parvovirus (CPV) see 2 below)

and thus the main route of infection is via secretions from infected animals. Some dogs may continue to shed the virus for several months if they survive initial infection and this has assisted the spread of the disease in local canine populations. In addition, assuming the epidemiology is similar in the feral fox, wherever the two species come into contact there is a risk of disease transfer. Historically, routine vaccination has successfully controlled the disease in most areas of the UK.

(a) Clinical signs of infection with virulent canine distemper virus

In general, three distinct clinical syndromes are recognised following canine distemper infection:

- (i) *Mild infection.* Affected dogs show only mild clinical signs such as a temperature rise (pyrexia), listlessness and a reluctance to eat for a period of time. Such generalised symptoms often go unremarked by the owner.

- (ii) *Generalised Infection.* This is the severe form of the disease and clinical signs are usually characteristic of the disease. Affected dogs may develop a discharge from the nose and eyes, become depressed and pyrexial. Some diarrhoea and sickness occur commonly. Characteristic chronic (later) signs include the development of thickened, highly keratinised pads on the feet (hence the term “hardpad” used to describe the disease) and in puppies defective enamel development (distemper teeth) on their permanent dentition is seen.

- (iii) *Nervous disease.* Dogs may develop encephalomyelitis (inflammation of brain and spinal cord) with variable presenting signs that tend to be progressive. Paralysis, seizures, ataxia and muscle spasms may be observed. A reported complication in chronic infections is “old dog encephalitis” in which a dog develops characteristic neurological signs months or years after apparently recovering from infection.

(b) UK authorised vaccines for canine distemper

- (i) Vaccines containing live attenuated CDV in combination with other vaccine antigens to protect against a range of other diseases are available. After primary vaccination in puppies between the ages of 6 and 12 weeks, recommended re-vaccination schedules for dogs range from 1-4 years according to the brand of vaccine used. With some UK vaccines, if used as recommended, there is no requirement to re-vaccinate dogs at twelve months of age as recommended in the WSAVA Guidelines. The WSAVA recommend a 12 month booster to ensure immunity for dogs that may not have adequately responded to the primary puppy vaccination course.

- (ii) For animals already infected with the virus, there are no specific medicinal products authorised for therapeutic treatment. Only supportive treatment can be given to dogs showing signs of disease. Administration of a vaccine once infection has occurred will not influence the development of the disease.

2. Canine Parvovirus (CPV)

- 2.1 In 1978 a new infectious disease appeared in dogs (Canine Parvovirus (CPV-2)) and developed into an epizootic affecting the entire canine population. Infection occurred in all ages of dogs and manifested itself in acute forms of infection that are now well recognised. As a new infectious disease in dogs, CPV demonstrated an epidemiology typical of a disease outbreak in a

population of highly susceptible animals (i.e. without any immunity). The emergence of parvovirus in dogs has been recently reviewed (Hoelzer & Parrish, 2010 *et al*) which confirms the origin of CPV-2 remains unproven despite various theories having been put forward to explain the emergence of the virus. In the intervening years, CPV-2 has undergone further evolution into a number of recognised sub-types or strains. CPV-2a appeared in the late 70s and CPV-2b in the mid-80s in the UK. A recently new variant CPV-2c appeared in 2000 and is thought to be the predominant virus variant in Italy and Germany and present at high rates in Spain (Decaro, 2008 *et al*) but to date CPV-2c has not been identified in the UK. CPV is endemic in the UK with recorded outbreaks of CPV-2, 2a and 2b. Despite the increasing number of sub-types there is a high degree of cross-protection between virus types and the current vaccines are considered to be protective against all of the currently known circulating strains of CPV (Truyen, 2006).

- 2.2. CPV is transmitted by direct contact with infected dogs or indirectly through faecal contamination. The virus is a very stable virus and can survive in the environment for many months. Therefore transmission does not necessarily require close contact between dogs and may be spread by transfer on clothing or other objects.

(a) Clinical signs of infection with virulent canine parvovirus

There are two predominant clinical syndromes associated with CPV infection:

- (i) *Enteric form. Enteritis* (inflammation of the small intestine). All ages of dog can be affected but it is most common in younger animals, especially pups. Mortality and morbidity depend on many factors but death can be very rapid in very susceptible individuals. Clinical signs include vomiting, diarrhoea and marked depression.
- (ii) *Cardiac form. Myocarditis* (inflammation of the heart muscle). This form of infection tends to occur in very young dogs when the heart muscle (myocardium) is still developing as the virus multiplies in rapidly dividing cells and the dam has no immunity to CPV infection. Clinical signs will vary depending on the severity of infection but range from sudden death to typical signs associated with heart failure.

(b) UK authorised vaccines for canine parvovirus

- (i) There are a number of authorised vaccines in the UK to protect against infection and these are listed in the attached table. All CPV vaccines currently authorised on the UK market are live attenuated vaccines and are frequently included with other antigens, in multivalent vaccines, to provide protection against a range of canine diseases. However, vaccines containing just CPV are also available. Details of the vaccination schedules recommended for puppies and older dogs are provided in the Table in Annex I. After primary vaccination in puppies between the ages of 6 and 12 weeks, re-vaccination schedules for dogs range from 1-4 years according to the brand of vaccine used. With some UK vaccines there is no requirement to re-vaccinate dogs at twelve months of age as recommended in the WSAVA Guidelines. The WSAVA recommend a 12 month booster to ensure immunity for dogs that may not have adequately responded to the primary puppy vaccination course.
- (ii) In addition to a wide choice of CPV vaccines there is also a specific product that has been authorised for the treatment of an active infection. Virbagen Omega is a novel product that has been authorised throughout Europe to reduce mortality and clinical signs of parvovirus (enteric form) in dogs and can be used in dogs as young as one month of age. Omega interferon is of feline origin and the exact mechanism of action is unknown but is thought

to enhance non-specific defences of the body against infection.

3. Canine Adenovirus (CAV)

3.1 Two closely related canine adenoviruses are associated with disease in dogs.

- (i) CAV-1 is infectious canine hepatitis (ICH) or “Rubarth’s disease” (named after the researcher who identified the infection in 1947). The cause is canine adenovirus 1 (CAV-1). The virus may also be associated with other forms of the disease including those affecting the respiratory system, kidney, the neonatal foetus and the eye (Appel, 1999).
- (ii) CAV-2 is associated with respiratory disease and, in unvaccinated dogs, is one of the potentially infectious viral agents that is involved in the disease complex called ‘Kennel Cough’.

3.2 The first modified live vaccines were derived from CAV-1 isolates in the 1950s but there were a number of unacceptable side effects associated with CAV-1 vaccines including ‘blue eye’ and kidney pathology. In the 1970s CAV-1 vaccines were replaced by CAV-2 based versions which not only provided protection against infection with CAV-2 but from CAV-1 infection, with the added benefit of a much reduced risk of adverse reactions, including ‘blue eye’.

3.3 Urine, faeces or saliva from infected dogs are the main sources of infection of ICH (CAV-1) and dogs who appear to have recovered from the disease may continue to shed virus in their urine for at least six months. CAV-2 is transmitted between dogs via the respiratory route. CAV-1 related disease has become uncommon in regions where routine vaccination is used effectively.

3.4 Clinical signs of infection with virulent canine adenovirus

- (i) **CAV-1.** Infection in unvaccinated dogs may lead to a severe form of acute hepatitis. Less acute forms of the disease are difficult to diagnose and dogs may present with only a mild pyrexia (increased body temperature) and inappetence. The abdomen is often painful due to the large inflamed liver. In severe cases, dogs are depressed, may vomit and die suddenly. If the disease progresses to a chronic form the animal is likely to become jaundiced due to extensive liver damage. The characteristic sign of ‘blue eye’ in an infected animal is caused by immune complexes that form in the cornea of the eye. It is usually a transient sign.
- (ii) **CAV-2.** CAV-2 virus is one of several infectious agents that may be involved in the disease complex commonly known as ‘Kennel Cough’. Infection is associated with laryngotracheitis producing the typical hacking cough. Symptoms are highly variable depending upon the variety of infectious organisms that become involved, with severe infections often leading to secondary bacterial infection of the lungs and trachea producing the pneumonia typical of the Kennel Cough syndrome. CAV-2 is considered to be one of the primary infectious agents that may trigger the onset of a Kennel Cough outbreak.

3.5 UK authorised products for canine adenovirus

- (i) There are a number of authorised vaccines in the UK to protect against infection and these are listed in the attached table. All CAV vaccines utilise live attenuated virus and are frequently formulated with other virus antigens, for ease of administration, to provide

protection against a range of canine diseases. Details of the vaccination schedules recommended for puppies and older dogs are provided in the Table in Annex I. After primary vaccination in puppies between the ages of 8 and 12 weeks, revaccination schedules for dogs range from 1-4 years according to the brand of vaccine used. With some UK vaccines there is no requirement to re-vaccinate dogs at twelve months of age as recommended in the WSAVA Guidelines. . The WSAVA recommend a 12 month booster to ensure immunity for dogs that may not have adequately responded to the primary puppy vaccination course.

- (ii) There are no specific products authorised for the treatment of affected animals and administration of a vaccine once infection has occurred will not influence development of the disease. Only supportive treatment can be given to dogs showing signs of disease.

4. Canine Leptospira

4.1 Leptospirosis is a serious bacterial infection of world-wide significance. The classification of this particular bacterium has undergone many alterations as there are a large number of antigenic types (called serovars), with some related serovars belonging to different bacterial species (Maele et al, 2008). The two most common leptospires that infect dogs in the UK are *L. canicola* and *L. icterohaemorrhagiae* and all vaccines in the UK incorporate these serogroups. However, in other countries different serovars have been indentified as being the important infections of dogs. These include *L. grippityphosa*, *L bratislava*, *L pomona* and, as a result, vaccines have been tailored to include these serovars. The epidemiology of these leptospires in the UK is largely unknown although some research is being undertaken to identify leptospire serovars circulating in foxes (personal communication). However leptospire organisms are known to affect several species of mammal including dogs, cattle, pigs, rats, foxes and man being relatively well known.

4.2 Leptospires are excreted in the urine of infected animals, symptomless carriers and maintenance hosts for months or throughout life. Rodents, in particular, are recognised carriers of some leptospiral serovars and, therefore, the organism is considered ubiquitous throughout the UK. Leptospires can survive well for many months in water and are considered to be common in waterways and ditches.

4.3 Infection can cause serious disease in many species and is a potentially life-threatening disease in humans. Weil's disease is a severe form of human leptospirosis leading to jaundice following liver damage and kidney failure. Leptospirosis was reported by 40% of UK veterinary practices in a recent industry survey (CICADA-Live survey, June 2009) covering a six month period. Leptospirosis is a notifiable disease and, on average, 40 human cases are reported each year in the UK. In 2007 there were 81 confirmed laboratory reports of leptospirosis in the UK. Further information may be accessed on the Health Protection agency website as follows:

http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733810062?p=1191942176648

4.4 The WSAVA Guidelines suggest that vaccination against leptospirosis should be restricted to geographical areas where a significant risk of exposure has been established or for dogs whose lifestyle places them at risk. Given the risks of infection to both dogs and their owners and the albeit limited information on the prevalence of disease in the UK, which suggests veterinary practices are seeing clinical cases, leptospiral vaccines are in effect commonly used, often in combination with core annual vaccination programmes by most, if not all, veterinary practices for the benefit of the canine and human population in the UK.

4.5 Clinical signs of leptospirosis

The clinical signs of infection with leptospira serovars in dogs are highly variable ranging from mild sub-clinical (hidden) infections to severe peracute (fatal) infections. The clinical signs of acute and subacute infections have been reviewed extensively by Maele (2008). Typical signs of infection include vomiting, lethargy, raised temperatures, abdominal pain and diarrhoea. Infection of the liver and the resulting chronic damage may lead to neurological signs and haemorrhaging into mucosa. Of particular concern is the chronic pathological damage to both liver and kidney caused by sub-acute and sub-clinical infection. This leads to both kidney and liver malfunction or failure in middle or old age.

4.6 UK authorised vaccines for canine leptospires

- (i) Leptospire differ from many of the other disease agents commonly found in canine vaccines because they are bacteria and not viruses. All UK authorised vaccines for use in dogs are products containing killed (inactivated) cultures or purified antigens of leptospiral organisms of the serovars *Leptospira interrogans icterohaemorrhagiae* and *L. canicola* to reduce infection, clinical signs and death. Inactivated vaccines in particular may contain various adjuvants to enhance the immune response. Leptospirosis vaccines are available for use either as stand alone vaccinations or in combination with other multivalent vaccines.
- (ii) As is characteristic for inactivated bacterial vaccines, the primary vaccine course for leptospiral vaccines requires two doses of vaccine administered 2-4 weeks apart to provide protective levels of immunity. In addition, annual re-vaccination is required to maintain protective levels of immunity. Laboratory challenge studies, used to support applications for a UK marketing authorisation, have demonstrated the degree of effectiveness of 12 monthly re-vaccination intervals. Published studies, using authorised products, add further support to the acceptance of a Duration of Immunity (DOI) of at least 12-14 months for several of the available canine leptospiral vaccines in the UK (Klaasen, 2003, Minke, 2009 *et al*).
- (iii) The WSAVA Guidelines recommend more frequent vaccination with leptospiral vaccines during the period of risk ranging from periods of 6-9 months.
- (iv) Unlike the viral vaccines, the circulating antibodies in the blood are relatively short lived following vaccination and, therefore, serological tests do not correlate well with protection and cannot be used reliably to indicate immunity.

4.7 **Canine para-influenza virus (CPi):** This virus is another of the infectious agents considered to be part of the group of organisms associated with the Kennel Cough syndrome (see also *Bordetella bronchiseptica* below). MLV vaccines exist in the UK for the control of infection with CPi and they are available in combination with other canine vaccine antigens to enhance protective immunity against respiratory disease or as part of a multivalent vaccines to protect against a number of core and non-core diseases. Vaccination reduces the severity of the clinical symptoms associated with respiratory infection. CPi vaccine is also capable in reducing the amount of viral shedding during infection and, therefore, reduce the capacity for infection spread. The immunity produced is relatively short-lived, compared to many of the other common canine vaccine components and annual or possibly more frequent vaccination is usually recommended.

4.8 **Bordetella bronchiseptica:** This is a bacterial, rather than viral, canine respiratory disease. However, unlike the inactivated bacterial leptospiral vaccines this is a live attenuated bacterial vaccine formulated to protect against associated respiratory infection. *B. bronchiseptica* infection is also one of the infectious agents in tracheobronchitis syndrome or Kennel Cough commonly seen in dogs. These vaccines are designed to be administered intra-nasally to stimulate a rapid, protective mucosal immunity against respiratory disease to prevent infection at the primary site of bacterial invasion. However, the duration of immunity for live attenuated mucosal vaccines is relatively short lived, with only up to one year's protection being provided following intra-nasal administration. Kennel Cough is a very common, multifactorial, contagious respiratory disease which results in a characteristic hacking cough and the potential for more serious pneumonic damage to the lungs. Generally, the cough can persist for weeks and can be life-threatening in puppies or animals with other medical complications. The agents responsible for Kennel Cough are spread through coughing or aerosol infection and are transmitted through close contact wherever dogs come together. Vaccination reduces the

severity of infection and the shedding of infectious particles but does not necessarily prevent infection.

OTHER UK VACCINES AUTHORISED FOR USE IN DOGS

5. **Canine herpes:** A purified sub-unit vaccine, containing glycoproteins of canine herpes virus adjuvanted in mineral oil, is available for the active immunisation of bitches to prevent mortality, clinical signs and lesions in puppies resulting from canine herpes virus infection. This is a specialised vaccine designed principally for use in breeding bitches. Puppies acquire the virus in the first few days following birth and infection results in serious illness and, in many cases, early neonatal death. The virus is one of the infectious agents believed to contribute to the condition of young puppies commonly called fading puppy syndrome. The primary course of vaccination consists of two doses of vaccine, the first administered during the bitch's season (or 7–10 days after the presumed date of mating) and the second injection is given within two weeks of the anticipated whelping date. The intent of vaccination is to generate antibodies in the early lactation of the bitch (colostrum) to provide the puppies with a maternally derived immunity to infection. Re-vaccination during subsequent pregnancies with the complete primary vaccination schedule is recommended. Canine herpes vaccines are not listed in the WSAVA Guidelines and are commonly used by dog breeders in bitches where the herpes virus is suspected of being the cause of early neonatal death. Herpes virus is transmitted between dogs chiefly in saliva and infection in the adult dog is associated with very mild or no clinical signs.
6. ***Babesia canis*:** An authorised vaccine formulated to protect dogs against infection with *Babesia canis* a protozoan parasite transmitted by ticks. The disease caused by this infection is Babesiosis which is not normally seen in the UK but is a risk for dogs travelling to other countries in the EU and further afield. In the last decade it has occurred more frequently in the UK as a result of changes to the legislation permitting dogs to travel abroad without the need for quarantine on return. The vaccine is intended for the active immunisation of dogs of six months of age or older against *Babesia canis* to reduce the severity of clinical signs associated with acute Babesiosis and, in particular, to reduce the severity and incidence of anaemia as a result of the destruction of red blood cells by this parasite. The vaccine contains a soluble parasite antigen from cultures of *B canis* and *B rossii*. The primary vaccination course consists of two doses administered 3-6 weeks apart. Re-vaccination is recommended every 6 months. *Babesia canis* vaccines are not listed in the WSAVA Guidelines.
7. **Canine coronavirus (canine enteric coronavirus) (CECOV)**

Authorised multivalent vaccines are available in the UK incorporating inactivated antigens intended to generate immunity to the enteric form of canine coronavirus infection. CECoV, as a primary agent, is associated with symptoms of mild enteritis, although more virulent strains have been identified. The virus can exacerbate infection associated other enteric pathogens, especially canine parvovirus in young dogs. Vaccination reduces infection with wild-type virus, of which there are two recognised genotypes (CECoV-I and II, Decaro *et al.*, 2009). Canine coronavirus vaccines are not recommended by the WSAVA Guidelines. A recent random survey of dogs presenting at veterinary practices in the UK revealed a prevalence of CECoV of nearly 3% (Stavisky *et al.*, 2010).

8. **Rabies virus:** Inactivated rabies vaccines are used in dogs primarily to meet the requirements of The Pet Travel Scheme (PETS). Rabies is a notifiable disease and a serious zoonosis (risk to human health). The UK is free of disease as a result of an historical eradication strategy and

stringent import controls on animals entering the UK. PETS is an official system that permits pet dogs, cats and ferrets from certain countries to enter the UK without quarantine as long as they meet the requirements of the PETS. It allows UK dog owners to travel to specified countries with their dogs and return with them to the UK. Under the scheme requirements, animals must be vaccinated against rabies virus and blood tested before they travel. Primary vaccination is usually a single dose providing a duration of immunity of up to 2-3 years. As a point of information, to permit effective epidemiological surveillance, rabies vaccines authorised for use in wildlife, are prohibited for use in the UK, despite being authorised by the EU.

- 8.1 Experience has shown that a proportion of vaccinated animals, while protected, may not show the required antibody titre on blood testing, which is a requirement of the PETS. Veterinary surgeons may consider two vaccinations, particularly in young, naive animals to overcome this problem. Blood sampling for antibody titres should ideally be carried out three weeks after the last vaccination.
- 8.2 Rabies vaccines are considered a core vaccine by the WSAVA Guidelines where vaccination is required by statute or in areas where the disease is endemic. However, in the UK they are only required for dogs travelling outside of the country and, therefore, rabies vaccination is not considered a core vaccine for the UK.

EPIDEMIOLOGICAL COMMENTS RELATED TO THE USE OF CORE AND NON-CORE CANINE VACCINES AND THE CONTROL OF THE ASSOCIATED DISEASES

9. There is limited information available on the incidence and prevalence of canine diseases driving the use of core and non-core vaccines of companion animals. However, the likelihood of wildlife reservoirs of infection, international travel, anecdotal evidence and veterinary knowledge strongly suggest that cases of these diseases do still occur and they cannot be expected to be eliminated despite many years of vaccination. For example, a recent research paper has shown the presence of Infectious Canine Hepatitis (CAV-1 infection) in red foxes in England (Thompson *et al*, 2010) and the wild animal reservoir can be expected to at least maintain the prevalence of CDV, CPV and leptospirosis. For the non-core diseases, several publications have shown a continuing high incidence of Kennel Cough particularly amongst dogs kept in or exposed to a kennel environment (Chalker *et al*, 2003; Erles *et al*, 2004; Erles *et al*, 2003).
10. An ongoing pharmaceutical industry funded project, CICADA (Computer-based investigation of Companion Animal Disease Awareness, www.cicadasurvey.co.uk), aims to collate information submitted by veterinary practices on numbers of both confirmed and unconfirmed (suspected) reports of major infectious disease. During the nine months leading up to March 2010 veterinary practices participating in this survey reported 1544 cases of Kennel Cough, 117 cases of canine parvovirus, 27 cases of leptospirosis, 2 cases of infectious canine hepatitis and 1 case of canine distemper. However, caution is needed in interpreting these data or using it to make decisions regarding vaccination due to the limitations in the way the data is collected and collated. For example, the veterinary practices which are participating may not be representative of all practices or regions in the UK as it is a voluntary reporting system. However, from these data it can be concluded that these diseases do still occur and still pose a potential threat to inadequately vaccinated dogs.
11. A Veterinary Products Committee (VPC) working group recommended in 2002 that manufacturers and other organisations should be encouraged to obtain data on disease incidence and duration of immunity in the field. A number of new initiatives should eventually improve the information available to veterinary surgeons and the pet owning public. An ongoing

collaborative project between veterinary schools, veterinary general practices and other partners in the UK involves the development of standardised nomenclature (www.venomcoding.org) and data coding in electronic patient records. This will enable the linking together of data from many different veterinary practices throughout the UK for the purposes of disease surveillance in companion animals. A second ongoing project, SAVSNET (www.liv.ac.uk/savsnet/), aims to collate laboratory results and to survey data from veterinary practices throughout the UK using the concept of 'one practice' management software. These projects should enable researchers to estimate disease prevalence in veterinary practice using client populations of companion animals.

12. However, it is important to be aware that this will only represent the population of dogs visiting veterinary practices, which in itself is a biased population. This population sample has a much higher probability of having been vaccinated regularly and, therefore, may not truly represent the general dog population which would include those dogs which have never visited a veterinary practice and have never been vaccinated. An under-representation of those dogs not visiting a veterinary surgeon may introduce bias into the results of the study, possibly making the prevalence of these diseases appear less frequent.
13. Epidemiological field studies to determine Duration of Immunity (DOI) can be carried out prospectively or retrospectively, each method having advantages and disadvantages. Prospective studies would need to recruit a large number of dogs and continue following each of these dogs for several years. Therefore, such studies are likely to be very expensive and there is a high potential of 'loss to follow-up' (e.g. owners moving house, dropping out of the study). Retrospective studies, where dogs could be recruited into the study based on the number of years since their last vaccination, are less resource intensive but rely more heavily on the use of questionnaires and accurate records. In both study types it would be important to look at other factors which are likely to confound DOI results. One significant factor, for example, would be the incidence (high or low) of a field challenge with an infectious organism. If a dog has been vaccinated and is then exposed to field challenge this is likely to boost the level of immunity and result in a perceived longer DOI. Therefore, in both study types, it would be necessary to obtain information from the dog owners about the lifestyle of their dogs in order to try to evaluate the effect of confounding factors. Epidemiological studies therefore can be of use in risk assessment in clinical circumstances but there are significant challenges to extrapolating these findings to the regulatory procedures to determine the DOI of specific vaccines.
14. There are also significant differences between individual animal vaccination programmes and population immunity. Both influence the risk of exposure to infection of the individual and thus the likelihood of disease. In its simplest form a population of vaccinated animals restricts the spread of an infectious disease and reduces the risk of exposure to infection. This benefits both vaccinated and unvaccinated animals. A vaccinated animal in a susceptible population may, however, be immune but may find its immunity overwhelmed by a challenge from a significant outbreak the disease.
15. Immunity therefore does not necessarily signify a freedom from disease. With some vaccines the ambition is simply to reduce the severity of the disease (e.g. Kennel Cough vaccine) rather than to protect fully the animal from the symptoms of the disease. In some cases the ambition is to reduce the dissemination of the disease causing organism.

AN OVERVIEW OF THE REQUIREMENTS FOR THE REGULATION OF VETERINARY VACCINES

16. Regulation in the EU

16.1 All canine vaccines on the UK market must meet the standards set by the Veterinary Medicines Regulations. This provides assurance that vaccine products have been manufactured to an acceptable quality, can be used safely both from the animal and owner perspective and achieve the level of protection claimed by the manufacturer. European legislation sets stringent technical standards for the manufacture and quality control of all veterinary vaccines. These requirements are laid down in Directive 2001/82 (as amended by 2009/9/EC), the European Pharmacopoeia and associated European Guidelines.

16.2 The Guidelines can be viewed on the European Commission website:

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-7/index_en.htm

16.3 Additional guidance has been developed by the Immunologicals Working Party of the CVMP:
<http://www.ema.europa.eu/htms/vet/vetguidelines/immunologicals.htm>

16.4 The mandatory requirements of the European Pharmacopoeia can be viewed at:
<http://www.edqm.eu/en/Work-ProgrammeStatus-607.html>

16.5 and the British Pharmacopoeia requirements are available at: <http://www.pharmacopoeia.co.uk/>

16.6 The Pharmacopoeias lay down minimum standards for specific veterinary vaccines and provide guidance on production, quality control tests and studies to demonstrate safety and efficacy.

16.7 The legal and technical framework for the manufacture and authorisation of vaccines has now been consolidated into two key pieces of EU legislation:

(i) Directive 91/412/EEC relating to the principles and guidelines of Good Manufacturing Practice (GMP);

(ii) Directive 2001/82 the legal framework for veterinary medicines in the EU as amended by 2004/28/EC and 2009/9/EC laying down the technical requirements.

16.8 Each and every authorised vaccine in the EU must be supported by its own specific data package submitted by the manufacturer. Each vaccine strain of a particular manufacturer is considered to have unique biological properties and, therefore, must have its own corresponding quality, safety and efficacy package to support the authorisation. The WSAVA Guidelines appear to assume common biological properties for certain groups of canine vaccines and could only be used to support data packages if applicants can demonstrate relevance to their particular vaccine product. An assumption that all vaccines are the same would ignore basic principles of immunology and vaccinology.

16.9 The rigorous controls applied to the manufacture of veterinary vaccine ensure that any potential risks to the animal, their owners and the environment are minimised. Veterinary vaccines are biological products that pose inherent risks owing to the source of starting material used for the manufacture of the vaccine. To illustrate this risk, vaccines are manufactured from seed materials in most cases originally derived from diseased animals. The seed materials are grown in cultures using a variety of biological materials, often sourced from animal tissues and, therefore, the risks of a vaccine containing an extraneous agent (unwelcome contaminant) are high. To prevent this, the manufacture of products according to the principles of Good

Manufacturing Practice (GMP), the application of quality control tests on every batch and pre-authorisation tests on seed materials are the principle controls to ensure the quality of authorised veterinary vaccines and the exclusion of extraneous agents.

- 16.10 The risks for killed/inactivated products are much reduced compared to the MLV vaccines. Principally this is because, during the manufacture of killed vaccines, the process of inactivation (a process using a chemical added to destroy the microorganism without affecting its ability to stimulate the immune system) should also destroy the majority of potential contaminants. Published reports of contaminated vaccines (Roth, 1999) causing disease in animals indicate that risks can be minimised but not eliminated. Continual improvement in the manufacture and controls applied to veterinary vaccines is the aim of both the industry and regulators.
- 16.11 Laboratory and field safety studies must be conducted for all vaccines before they are marketed. Laboratory studies are designed to demonstrate the safety of the vaccine in the youngest puppy intended for vaccination or any special categories of dog that are to be included in the authorisation, such as pregnant bitches. Such tests use a single dose, an overdose and repeated doses to cover all potential safety concerns when administered by the veterinary surgeon in the field. The studies are designed to evaluate the local and systemic reactions following administration of the vaccine to the most sensitive groups. Any observed reactions are described on the publicly available SPC (Summary of Product Characteristics): <http://www.vmd.gov.uk/ProductInformationDatabase/Default.aspx>
The most common are local injection swellings which resolve in a few days. More severe reactions are possible but extremely rare. Nevertheless, all potential adverse reactions of this type are taken into account when deciding whether to authorise the vaccine.
- 16.12 For MLV vaccines there are additional studies to investigate the possibility of the vaccine organism reverting to virulence (and producing a clinical infection) and any potential to disseminate within the animal or, more seriously, to spread into the environment and thus prove a risk to other animals and humans. Once completed satisfactorily the laboratory studies are followed by field studies to confirm the safety profile established during the laboratory studies and in addition, using a range of breeds and much larger numbers of animals. Specific safety studies may be required under the guidance within the European Pharmacopoeia. One example would be the requirement to demonstrate any immunosuppressive property (depression of the natural immune system) of a particular vaccine strain. This is a natural property of some pathogenic strains of viruses. There are specific European Pharmacopoeial monographs for CDV, CAV, CPV, CPi and canine leptospirosis that establish minimum standards for quality, safety, potency and immunogenicity.
- 16.13 Laboratory and field efficacy studies are also performed to demonstrate the onset and duration of immunity of the vaccine. To establish the onset of immunity, puppies at the minimum age for vaccination receive a primary vaccination course and the time interval to develop a protective immune response is established by either viral challenge or serology. This period is usually one to two weeks but can occur more rapidly for mucosal (e.g. nasal) vaccines such as those authorised for preventing Bordetella infections (Kennel Cough). Maternal antibodies found in young puppies may interfere with the immune response to a vaccine and manufacturers must demonstrate the ability of their vaccine strains to overcome the neutralising effects of these antibodies. As a result of these studies the effects of maternally derived antibodies (MDA) on the recommended vaccination schedule will be evaluated to determine the age by which the vaccine can be expected to be effective in pups. Vaccination schedules are designed to minimise the risk of puppies acquiring a clinical infection, taking account of MDA and the risk of acquiring the disease from the environment. Primary vaccination schedules in puppies are usually completed between 10-12 weeks of age, although this may be delayed where MDA levels are high. The WSAVA Guidelines offer general advice on this and recommendations made there can be applied, taking account of local epidemiological information, the vaccine used and veterinary advice.

16.14 The DOI established through research is a minimum period of duration and the actual DOI may be much longer. However to establish the maximum duration of immunity that might be applied across the wide range of husbandry systems would require animals to be isolated for very long periods of time and this raises considerable concerns about animal welfare, veterinary ethics and cost. Any scientific research should only be conducted where the benefit to the wider population of animals can be justified. Therefore, extending any laboratory studies to derive DOI beyond 3-4 years poses significant questions as to the value of such studies and the benefit they would offer to the wider population of pet animals.

17. **Public information and transparency**

17.1 Since October 2005 regulatory authorities have been required to prepare and publish Public Assessment Reports (UKPARs) which provide information on the manufacture of the vaccine and the scientific studies that were assessed to support the safety and effectiveness of the product. For UK authorised vaccines, public assessment reports (UKPARs) are available for all canine vaccines authorised after October 2005 on the VMD website (www.vmd.gov.uk) and the EMA website <http://www.ema.europa.eu/htms/vet/epar/eparintro.htm> publishes European Public Assessment Reports (EPARs) for canine vaccines authorised by the European Medicines Agency.

17.2 Some reports may be accessed through the Heads of Medicines Agency website, where another EU Member State led on the scientific assessment of a particular product (PuAR): <http://www.hma.eu/vmri.html>.

COMPARISON OF UK AUTHORISED VACCINATION SCHEDULES WITH THE WSAVA GUIDELINES

18. The Summary of Product Characteristics (SPC), a publicly available document produced during the authorisation of a veterinary vaccine, provides guidance on the authorised use of the product and includes information which may help the veterinary surgeon when prescribing the product. SPCs for UK authorised products are available on the VMD's website www.vmd.gov.uk in the Product Information section, and on the European Medicines Agency (EMA) website for products authorised via the European centralised system <http://www.ema.europa.eu/htms/vet/epar/eparintro.htm>.

19. The WSAVA Guidelines (<http://www.wsava.org/SAC.htm>) were developed by a panel of veterinary experts and are based on experience, expert opinions and scientific data that may or may not have been published. They are general Guidelines intended for world wide interest and are not written with reference to data packages for specific vaccines. These Guidelines provide useful guidance to clinicians but should be read in conjunction with the specific product SPC. The WSAVA Guidelines are, therefore, supplementary information to UK authorised vaccine SPCs and for the most part are complementary. The work that supports the recommendations in the WSAVA Guidelines has been reviewed by Schulz (Schultz, 2006, 2010, Schulz *et al.*, 2010).

20. A critical issue is the duration of immunity of core MLV vaccines. The recommendations for use of the MLV components of most UK authorised products are in general accord with the re-vaccination schedules recommended in the WSAVA Guidelines. However, there are instances where a conflict might be perceived to exist in terms of vaccination schedule recommendations.

20.1 For example:

- (a) For primary vaccination of puppies the WSAVA recommend up to three doses of vaccine. The majority of UK vaccines recommend two vaccinations for the puppy.
- (b) The WSAVA Guidelines recommend a booster at 12 months after completing the primary vaccination for all core-components (defined as canine distemper, parvovirus and adenovirus) followed by a booster vaccination frequency of not more than every three years. For UK authorised vaccines this is only included on some SPCs where the data submitted indicated that a first annual booster is necessary; for other products, the interval recommended between booster vaccinations following the primary course of vaccination is 3 or 4 years. However, whatever the SPC states, a veterinary surgeon should take account of the recommendations and warnings on the SPC alongside any specific risk factors for the individual animal when devising the optimum vaccination schedule for the young adult. This may follow either the recommendation for a first full yearly booster, as may be specified in the SPC of some products and WSAVA Guidelines, or this may prove to be unnecessary.
- (c) The WSAVA Guidelines state that, because of the presence of maternally derived antibodies, the immune response to vaccination before 12 weeks of age is likely to be weak and suggest that, where animals are vaccinated so that the primary course of vaccination is finished by 10 weeks of age, caution is required in terms of the exposure of these animals to other animals. There are a number of UK authorised products with SPCs which specify a primary course of vaccination that ends at a minimum age of 10 weeks. These claims will have been supported by data demonstrating the ability of the vaccine to overcome the inhibitory effects of maternally derived antibodies. However, should a veterinary surgeon choose to observe the advice in the WSAVA guidance, the SPC does not preclude the administration of the vaccine to puppies older than the minimum age stated on the SPC. There are appropriate warnings concerning the need to take into account the effect of the presence of maternally derived antibodies (MDA), especially if the levels are expected to be high. For some products there are recommendations to delay starting the vaccination course if high levels of MDA are expected. All of these statements will be supported by suitable data.
- (d) The WSAVA Guidelines recommend that the primary vaccination schedule consists of three vaccinations finishing at 14-16 weeks of age. SPCs for vaccines in the UK usually recommend two vaccinations. Data will have been presented to the VMD to demonstrate the effectiveness of two vaccinations in both sero-negative puppies and those with levels of maternally derived antibodies that reflect the levels expected in the field. Veterinary surgeons can, however, make their own risk assessment and decide to administer a third vaccination where they consider this necessary.
- (e) The WSAVA Guidelines do not recommend the use of canine coronavirus (CCV) vaccines as the prevalence of clinical cases of confirmed CCV disease does not justify vaccination. For authorised canine vaccines containing either CCV or a strain of feline corona virus (FCV) the benefit/risk assessment was considered favourable during assessment of the product.
- (f) The WSAVA Guidelines recommend re-vaccination intervals for canine leptospira vaccines of 6-9 months during a period of risk. The UK authorised products for leptospira recommend annual revaccination and this reduced frequency of vaccination is justified by the data supporting the vaccine authorisation.

SPCs. However, some account of the WSAVA Guidelines may be taken by, for example, giving a full first annual booster before applying the extended duration of immunity claims, or by delaying the second puppy vaccination until the animal is at least 12 weeks of age where, for example, levels of maternally derived antibodies are expected to be high.

22. The WSAVA Guidelines include claims for DOIs of seven years or longer for CPV-2 and CDV MLV vaccines. The DOI for CAV-2 vaccines is claimed to be up to three and seven years for canine respiratory disease complex and infectious canine hepatitis respectively. Much of the work to support these extended claims, beyond the 3-4 years established by most manufacturers, has been reviewed (Schultz, 2006, 2010). He has reported studies assessing the minimum duration of vaccinal immunity in more than 1000 dogs vaccinated with products from all the major US veterinary biological companies, using either serology or challenge in selected groups. For CDV, CPV and CAV, antibodies are suggested to be well correlated with protection, with the mere presence of antibodies in actively immune dogs demonstrating protective immunity.
23. These studies were conducted in dogs kept in their natural, as well as virus-free, environments. The longest period of time that antibodies have been shown to persist in natural environments is 14 years for CDV, 14 years to CAV-1 and 10 years for CPV-2. In environments free from virus, protection from challenge has been demonstrated 9 years post-vaccination with CDV and CPV-2 with antibodies persisting for this period at levels not significantly below titres following primary vaccination. The minimum established DOI for CAV-2 vaccines appears to be 9 years based on serology and 7 years with challenge. For CDV there appears to be a suggested strain variation with Rockborn or Snyder Hill strains having extended DOIs compared to vaccines produced using Onderstepoort strains.
24. Confounding these observations and claims is the lack of detail reported in the primary scientific literature for these studies and as a result a thorough scientific analysis of the data is not possible without the provision of the raw data. For example, it is not possible to ascertain the number or age of the puppies at the time of vaccination, their immunological status or the vaccination protocol and products administered. The serological methods are not described, nor are the clinical signs or the detailed observations following challenge. Whilst the evidence as reported is persuasive, much of the data would not meet the usual standards of scientific scrutiny reserved for peer reviewed primary literature.
25. It is, however, recognised that there is an increasing body of scientific literature and opinion that suggests the DOIs of the core vaccines (as defined by the WSAVA Guidelines) for dogs may be considerably longer than the authorised claims for existing vaccines on the EU market. Nevertheless regulatory and scientific requirements restrict extrapolation of generic claims, like the data discussed, to specific products. Despite this conflict, veterinary surgeons in the UK may take account of recommendations in the WSAVA guidelines and scientific journals when devising optimum vaccination schedules for their clients' pets. However a shift to a revised vaccination regime that proved ineffective in maintaining the control of any of the diseases mentioned could be disastrous for a community of pet animals.

SAFETY OF CANINE VACCINES, ADVERSE REACTION AND VACCINE FAILURES

26. The VMD's Pharmacovigilance system

- 26.1 European veterinary medicines legislation is designed to ensure that decisions on whether a product is safe and effective for use in either food producing or companion animals are based on robust science. Recent changes in European veterinary medicines legislation have placed greater emphasis on pharmacovigilance which has been defined by the World Health

Organisation as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any medicine-related problem.

- 26.2 Since the relationship between an adverse effect and the use of an individual veterinary medicine may be largely circumstantial, the basis of veterinary pharmacovigilance is the identification of reporting trends. One of the aims is the detection of new safety signals in relation to the use of a veterinary medicine. A signal consists of information about a possible causal relationship between an adverse event and a veterinary medicine, the relationship being previously unknown. The regular review and analysis of adverse events in a pre-defined time period for one specific product in a particular species might lead to the identification of potential signals when, for example:
- (a) an increase in the number of adverse events in a short period is observed;
 - (b) an increase in the frequency of a particular clinical sign is recorded, compared with the expected frequency for that sign;
 - (c) a clinical sign not previously associated with the product is reported.
- 26.3 Pharmacovigilance databases are designed for surveillance not for detailed epidemiological investigation. Acute reactions which develop over a short period are more likely to be detected than chronic problems taking months or even years to become apparent. In the latter case there could be a number of confounding factors making it difficult to conclusively establish a causal relationship between the veterinary medicine and an adverse effect. Specific epidemiological studies may be necessary to answer certain questions.
- 26.4 In the case of vaccine induced adverse reactions, to detect changes in the incidence of rare events requires large representative samples of both vaccinated and unvaccinated control animals to be compared in order to have sufficient statistical power to prove conclusively that the reported effect is due to vaccination. This is likely to be difficult to achieve, given the high numbers of vaccinated animals in the UK.
- 26.5 For a veterinary medicine to be considered safe, its expected benefits should be markedly greater than any associated risks of harmful reactions. All veterinary medicines can cause reactions; however, it is important to note that most animals treated with veterinary medicines suffer no observable serious side effects. Idiosyncratic drug reactions occur with veterinary medicines as they do with human medicines. Such reactions cannot be explained by the known mechanisms of action of the agent involved and develop unpredictably in susceptible animals only. Such reactions are generally thought to account for up to 10% of all adverse reactions in human medicine. They are difficult to study because of their sporadic nature and the lack of valid models. While the mechanism of most idiosyncratic drug reactions is thought to be immune mediated toxicity, they are not confined to immunological products.
- 26.6 The fact that both immediate and longer term adverse events may occur make the benefits of vaccination for a healthy animal more difficult to assess especially as the prevalence of a disease against which a vaccine will protect may not be measurable with any degree of certainty. In such cases a decision regarding vaccination of a healthy dog is largely a matter of judgement on the part of the owner following advice from their veterinary surgeon. It is acknowledged that more information is needed on the prevalence of canine diseases in the UK to enable veterinary surgeons and their clients to make more meaningful benefit/risk assessments on whether to vaccinate an individual animal.

- 26.7 Data on adverse reactions reported to the VMD involving different types of veterinary medicines are published annually in the SARSS report in The Veterinary Record
<http://www.vmd.gov.uk/Publications/SARSS/SARSS.htm>. Quarterly summaries of adverse reactions reported to the VMD are published on the VMD website
<http://www.vmd.gov.uk/SARQuartSummaries/default.htm>.
- 26.8 Over 82 million doses of the vaccines currently available on the UK market have been sold for use in dogs since 1985 and there have been less than 7,000 reports of adverse events as a result. It is acknowledged that any pharmacovigilance system is primarily reactive and under-reporting is an inevitable feature. However, under-reporting will apply equally to all products and given that changes in the incidence rates of adverse events are the useful indicators of issues which need to be investigated, it is the clinical detail in the reports and the trends and patterns of adverse events that are far more important tools in the science of pharmacovigilance. Therefore under-reporting is not a significant issue. Nevertheless, this does not mean increased levels of reporting should not be encouraged.
- 26.9 Whether investigating emerging issues or generating pharmacovigilance-based information, the VMD has access to the Eudravigilance Veterinary system, a European network enabling the electronic exchange of pharmacovigilance data and its storage in a central European database where it is available to all member states. This expands the database available to assess the significance of adverse reaction reports.
- 26.10 Further information on the VMD's Pharmacovigilance system can be found in Veterinary Medicines Guidance Note 13:
<http://www.vmd.gov.uk/General/VMR/vmgn/VMGNote13.pdf>

27. Analysis of suspected adverse reaction reports for canine vaccines in the UK

- 27.1 During the period 2005-2010 (to date), 12.9 million doses of dog vaccines were sold in the UK and 2,392 adverse reactions were reported from the use of authorised dog vaccines. This represents an incidence rate of 18.5 per 100,000 doses (0.0185%).
- 27.2 Table 1 includes the reported reactions for the most common disorders archived within the VMD's pharmacovigilance database. The structure and terminology used in the table reflect the EU system of recording adverse events. The Table only includes cases where there is a definite or possible association with the product and it should be noted that each report may be associated with more than one animal and more than one case may be attributed to each animal.
- 27.3 The most frequent reports in the total of 2,392 adverse reactions are for systemic disorders. Table 1 divides into the cases into five basic categories and lists the most frequently reported individual cases in each one.
- 27.4 Of the 2,392 Suspect Adverse Reaction (SAR) reports received by the VMD, 25 have been associated with immune mediated complications.
- 27.5 The purpose of pharmacovigilance is to protect animal health and to ensure the balance of benefits and risk remains favourable. Adverse reactions to canine vaccines are rare with less than 18.5 reports per 100,000 doses. Whilst acknowledging a level of under reporting that is unquantifiable, the benefits of vaccination are considered significantly greater than the risks of infection of the ever present canine infectious diseases in the UK.

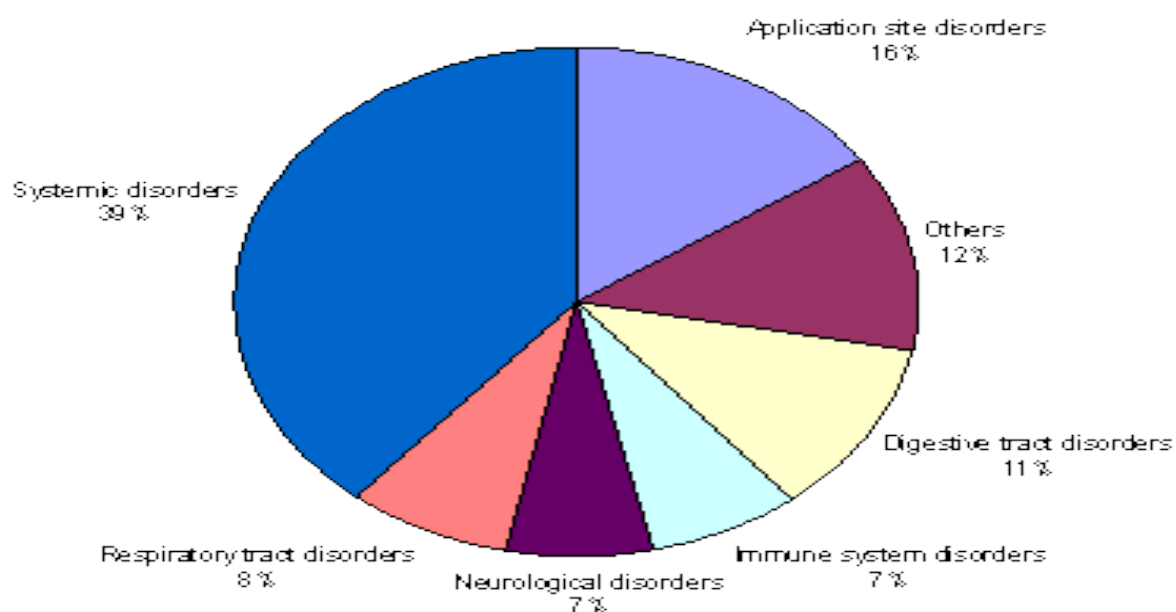
Table 1. Adverse events recorded 2005-2010 for UK authorised dog vaccines. The Table includes the most frequently reported clinical signs for the five most common System Organ Class disorders (SOC).

	Number of cases	Incidence Rate per 100 000 doses sold
1. Systemic disorders		
Lack of efficacy	523	4.1
Lethargy	450	3.5
Pyrexia	230	1.8
Death	180	1.4
Anorexia/inappetence	170	1.3
2. Application site disorders		
Injection site oedema	380	2.9
Injection site abscess	170	1.3
Injection site pain	140	1.1
3. Digestive tract disorders		
Emesis (vomiting)	315	2.4
Diarrhoea	180	1.4
4. Respiratory disorders	400	3.1
5. Immune System Disorders		
Allergic oedema	190	1.5
Hypersensitivity	85	0.66
Anaphylaxis	70	0.54

Urticaria	30	0.23
Immune mediated disorder	25	0.19

Figure 1.

Percentage breakdown of SARs by System Organ Class (SOC) reported to dogs post vaccination



28. **Veterinary Products Committee (VPC) Working Group on Feline and Canine vaccination 2002**

- 28.1 The Working Group was set up by the Veterinary Products Committee (VPC) in response to concerns in both the public domain and scientific community about possible health risks related to the routine vaccination of dogs and cats. The working group concluded that vaccination plays a very valuable role on the prevention and control of the major infectious diseases in cats and dogs. Although adverse reactions to vaccination occasionally occur, including lack of efficacy, the Working Group concluded that the overall risk/benefit analysis strongly supports their continued use. <http://www.vpc.gov.uk/Working/feline.html>
- 28.2 The Working Group also observed that there was evidence to support a longer duration of immunity following vaccination than the one year which, at that time, was typically recommended on the product literature.

29. **Practice Overview of Canine Health (POOCH) 2004**

- 29.1 In 2006, the Animal Health Trust published the results of an epidemiological investigation into whether there was a temporal association between canine vaccination and ill-health. Random selections of dogs were evaluated from a number of veterinary practices in order to evaluate whether there was an increase for ill-health in dogs receiving a recent vaccination. Nearly 4,000 questionnaires were received from 28 veterinary practices. Within three months of vaccination, there was no significant association with ill-health. The study did not attempt to address the health status of vaccinated versus non-vaccinated dogs due to the difficulties in identifying a sufficient number of unvaccinated animals registered with veterinary practices (Practice Overview of Canine Health [POOCH], Edwards *et al* 2004).
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VACCINES, IMMUNOLOGY AND DURATION OF IMMUNITY

30. **Modified Live Virus (MLV)**

- 30.1 A vaccine is generally defined as a formulation of live attenuated organisms, killed organisms or other antigens designed to elicit an immune response in an animal to protect against infection, clinical signs or mortality from infectious diseases. With the emerging development of live recombinant vaccines the distinction between conventional MLV and killed vaccines is less obvious, with the recombinant vaccines behaving in many respects like MLV vaccines but with few disadvantages. There are currently no live recombinant vaccines authorised for dogs on the UK market.
- 30.2 Conventional MLV vaccines have a number of advantages over killed vaccines and have been mostly produced for viral diseases owing to the relatively ease at producing stable attenuated products. The only live attenuated bacterial vaccines marketed in the UK are for Kennel Cough caused by *Bordetella bronchiseptica*. MLV vaccines, in general, produce a more rapid onset and longer duration of immunity compared to killed products probably because the immune response to MLV vaccines more closely mirrors the response to infection with disease and, therefore, a strong active immunity is produced in the vaccinated animal. Killed vaccines may incorporate an adjuvant to enhance the immune response and usually require a two-dose primary vaccination course to achieve the required level of protection.
- 30.3 The main risk for MLV vaccines is their potential to revert to virulence and cause disease in

vaccinated animals. Such vaccines would pose a greater potential risk to pregnant or immunosuppressed animals. MLV vaccines also tend to be less stable if stored incorrectly and pose a greater risk of being contaminated with other undesirable microorganisms.

31. Notes on the immune response to vaccines

- 31.1 The immune system can be broadly divided into the innate and adaptive immune systems. Interaction between the innate immune system, which responds quickly and non-specifically to a pathogen and the adaptive immune response, which acts in an antigen-specific manner, is essential for the induction of an effective immune response to pathogens (Palm and Medzhitov, 2009).
- 31.2 Most vaccines do not prevent infection but reduce the severity of the illness associated with disease. A live vaccine contains a virus that has been modified to lose its disease-causing ability (attenuated). Killed vaccines are attenuated through a process that results in their death.
- 31.3 In general, the live viruses in MLV vaccines undergo limited cycles of development within the animal. They provide rapid protection and can overcome circulating maternal antibodies more effectively than inactivated vaccines because they are structurally very similar, or in many cases identical, to the disease causing pathogen and undergo a similar development within cells. In addition, they stimulate the correct type of immune response, providing protection for long periods. The main disadvantages of MLV vaccines include the possibility of reverting to a disease causing form and the possibility of producing disease in immunocompromised patients. Killed vaccines have the obvious advantages of being safer in immunocompromised patients and not reverting to virulence. However, they are generally not processed by the immune system in the same way as the live organism and, therefore, do not stimulate strong immune responses. As they don't stimulate the complete immune response they require the addition of adjuvants (non-specific immunostimulants) and require frequent re-vaccination to maintain immunity.

32. Immunological memory

- 32.1 Immunological memory is the ability of the adaptive arm of the immune system to recognise and respond more rapidly to an antigen that it has encountered previously (Zinkernagel *et al*, 2006). The protective immunity provided by vaccines is dependent on the magnitude and nature of this response. The response can be best measured by controlled challenge studies, testing the immunity of a vaccinated animal by inoculating live pathogenic organisms. However, the ultimate determination of a vaccine's merits comes from controlled tests conducted under field conditions. Antibodies have a short half-life and continual replenishment is required to maintain stable long-term protective immunity characterised by high levels of neutralizing antibodies (Wrammert and Ahmed, 2008). Despite the importance of long-lived antibody responses, relatively little is known about how the response is maintained. The mechanisms by which long-lived immunity is maintained are currently active fields of research.

33. Serology as an alternative to vaccination

- 33.1 Serology is the qualitative or quantitative diagnosis of antibodies to a particular disease organism or antigen in serum. Serological tests are used to diagnose infection or determine the immunological response to a vaccine. Serological surveys may be used in epidemiological investigations to determine the prevalence of a particular disease in the field.
- 33.2 Serological tests can be used to measure the antibody-mediated immune response to many

disease organisms or vaccines and are becoming increasingly used to determine whether a vaccinated animal is protected to reduce the frequency of re-vaccination as a result of perceived associated risks. Interpreting the serological titre to determine protection to a particular disease is dependent on the ability to correlate the results derived from a particular test with protection. For CDV, CPV and CAV there appears to be a relatively strong correlation between neutralising antibody titre and protection (VPC Working Group, 2002). Yet perversely, animals with high levels of circulating antibody may still be susceptible to infection, whilst some animals may be protected even in the absence of antibodies.

- 33.3 Serology is used extensively in human medicines to assess DOI of some vaccines where protective levels of antibody are known, as it is not possible for ethical reasons to conduct challenge studies. Thus standardised and validated *in vitro* serological tests that correlate with protection are available to determine the immunological status of a patient. In the veterinary field DOI is usually established by challenge; the “gold standard” for demonstrating protection from infectious disease. Unfortunately, there are no international standards or prescribed serological tests for most of the canine diseases. Tests vary considerably between laboratories and are difficult to standardise. Diagnostic laboratories must validate their own in-house tests and establish thresholds for re-vaccination based on their expertise and scientific opinion. In the absence of clearly defined protective titres, interpretation of serological tests must be treated with care and advice sought on equivocal results. Whilst the WSAVA Guidelines suggest any measurable titre in an actively immune vaccinated animal is correlated with protection, the evidence to support such conclusions appears weak.
- 33.4 Serological testing as an alternative to vaccination has been reviewed by several notable experts in the field of veterinary diagnostics (Burr, 2006, Tizzard, 1998, Twark, 2001, Ottiger 2006, Dodds 1999 *et al*). *In vitro* tests, such as virus neutralisation tests (VNT) and haemagglutination inhibition tests (HIT), are preferred techniques as they measure functional aspects related to virus infection. Enzyme-linked immunoabsorbent assays (ELISAs) have a number of advantages over VNT and HIT but do not necessarily measure titres of neutralising antibodies. Thus the basis of a test can be an important consideration before interpreting the results.
- 33.5 The conclusion has to be that serology provides useful additional information on the immune status of an animal but should not be treated in isolation to other determinants for deciding upon re-vaccination. The fact that a particular titre may be well correlated with protection does not ensure the animal is protected. The application of statistical correlations to the individual will, by the very nature of statistics, expose some to the risks of disease. The risks of over-vaccination are arguably relatively small compared to the risks of exposing susceptible animals to life-threatening infections.

34. Vaccine-induced auto-immune disease

- 34.1 Immune mediated diseases and the association with vaccine reactions have been reviewed by Day (1999, 2006), Pedersen (1999) and the VPC Working Group (2002). Vaccine reactions are generally classified into one of four recognised categories: Type I-IV. The immunological theories behind such reactions would suggest that such adverse events should only occur following an immunological reaction to a previously exposed vaccine antigen, adjuvant, excipient or other production remnants such as bovine serum. However, immune mediated reactions can also follow the administration of a primary dose of vaccine and the exact mechanisms for such a reaction are unknown.
- 34.2 Type I hypersensitivity reactions involve an immune mediated reaction that releases potent inflammatory mediators and other chemicals that trigger an anaphylactic reaction in the affected animal. The reactions are usually acute, with the clinical signs appearing within minutes or hours of vaccination. Typical signs reported are facial oedema, shock, lethargy, respiratory

distress and diarrhoea. Severe anaphylactic reactions may result in death. Urticaria (hives), facial oedema and anaphylactic shock are specific clinical manifestations of Type I hypersensitivities.

- 34.3 Type II hypersensitivity reactions involve the binding of the animal's own antibodies to cells or a cell matrix. The formation of auto-immune antibodies is thought to involve a number of complex immunological mechanisms. Secondary immune mediated haemolytic anaemia (IMHA) has been associated with vaccination but may also occur following infection, neoplasia or administration of medications. In this condition, auto-antibodies are produced against the animal's own red blood cells but the immunological mechanism by which vaccines may produce such a response is not yet established. Confirmation of IMHA is dependent on the demonstration of auto-antibodies and, therefore, not all reports of such adverse events can be recorded accurately if confirmatory diagnostic tests have not been performed. For the period 2005-2010, 57 suspect adverse reaction reports of immune mediated reactions were submitted to the VMD. Subsequently only 25 of these reports were attributed to immune mediated reactions. Other clinical manifestations of Type II disease include immune mediated thrombocytopenia (IMTP) (autoantibodies to blood platelets) myasthenia gravis (autoantibodies to muscle nerve receptors) and pemphigus (foliaceus & vulgaris) (auto-antibodies to epidermal proteins).
- 34.4 Type III hypersensitivity reactions result from the formation of circulating complexes of antigen and antibody that deposit in certain organs or tissues in the body leading to inflammatory reactions and destruction of cells and associated matrix. The deposition of immune complexes usually results in inflammation of the blood vessels. The reaction is dependent on the continued presence of both antibody and antigen with the latter being derived from infection, vaccination, medication or exposure of 'self-antigens' through disease. Infections will inevitably result in the formation of immune-complexes as the body aims to rid itself of a foreign invader. Some examples of well known immune-complexes provide clinical signs such as:
- (i) 'Blue Eye' is a well documented manifestation of a Type III reaction following infection with CAV-1 and or administration of some of the early CAV-1 vaccines. Replacement of CAV-1 by CAV-2 vaccines have minimised the risk of such adverse events with just six reports of 'blue eye' reported to the VMD during the period 2005-2010.
 - (ii) Reactions involving type III immune mediated mechanisms have also been demonstrated following rabies virus vaccination.
 - (iii) Systemic lupus erythematosus (SLE), a disease characterised by the development of antinuclear antibodies (ANAs).
 - (iv) Drug-induced arthritis has been reported as a Type III reaction but the evidence of similar vaccine associated immune-mediated syndrome is sparse. The VMD has received two reports of pemphigus associated with vaccination during the last five years.
- 34.5 Type IV hypersensitivity reactions or "delayed-type hypersensitivity" are cell, rather than antibody, mediated. These diseases are usually relatively slow to develop and are dependent on the cell-mediated arm of the immune system.

ADDITIONAL POINTS

35. Position of the British Small Animal Veterinary Association (BSAVA)

- 35.1 The BSAVA produced a policy statement on companion animal vaccination in 2007.
- 35.2 The BSAVA endorsed the Veterinary Products Committee (VPC) report (2002) and the Committee for Veterinary Medicinal Products (CVMP) statement (2003) on canine and feline vaccination, and advised members that they should consider the recommendations made in these reports when discussing with owners the relative risks and benefits of vaccination policy.
- 35.3 The BSAVA is a member organisation of the WSAVA and endorses the vast majority of WSAVA Guidelines for the Vaccination of Dogs and Cats (2007).
- 35.4 The BSAVA believes that vaccination plays a very valuable role in the control of infectious disease in cats and dogs. It recognises that adverse reactions, including lack of efficacy, may occasionally occur but that the overall risk/benefit analysis strongly supports the continued use of vaccination to control major infectious diseases of cats and dogs. The BSAVA strongly supports the concept that a thorough risk/benefit assessment on an individual case basis should be discussed with clients when deciding on timing of vaccination and use of particular vaccines for particular animals. The BSAVA strongly supports all scientifically valid research into the epidemiology, control and prevention of canine and feline infectious diseases in the UK and the publication of such research, so as to provide veterinary surgeons with appropriate information on which to base decisions. The BSAVA strongly supports further research into improving efficacy and safety of vaccines.
- 35.5 The BSAVA supports the use of the wide range of high quality, safe and efficacious licensed veterinary vaccines. The BSAVA believes that all animals should receive the benefit of solid protective immunity from life-threatening infectious diseases that is conferred by vaccination using licensed veterinary products. The BSAVA endorses the concept that tailored vaccine programmes should be applied to as many animals as possible within a population to maintain the level of protective immunity within that population.
- 35.6 The BSAVA strongly endorses the importance of pharmacovigilance and the VMD's Suspected Adverse Reactions Reporting Scheme.

36. Animal Boarding Establishments and vaccination requirements

- 36.1 The VMD does not regulate the vaccination requirements laid down by animal boarding establishments. Local Authorities issue licences to proprietors of boarding kennels and catteries under the provisions of the Animal Boarding Establishment Act 1963. The licence can stipulate a number of conditions to secure the health of welfare of animals kept at the establishment. Animals must be kept in suitable and secure accommodation, supplied with adequate food and fresh drinking water and visited at regular intervals. In addition the licence may stipulate that reasonable precautions are taken to prevent the spread of infectious diseases and parasites.
- 36.2 The 1963 Act does not specify specific vaccination requirements for animals to be admitted to boarding establishments. The vaccination related conditions are introduced under section 1 (2.c) where it is stated that "that all reasonable precautions will be taken to prevent and control the spread among animals of infectious or contagious diseases...". Anyone unhappy with the decision to refuse a licence or the conditions attached to the licence has the right to appeal. Businesses handling animals such as boarding establishments may also be covered by other pieces of legislation such as the Animal Welfare Act 2006, Welfare in Transport Order 2006 and health and safety legislation.

- 36.3 In 1993 The Chartered Institute of Animal Health published comprehensive guidance and model licence conditions such that a consistent approach was maintained in the issuing of licences and the enforcement of the legislation by authorities.
- 36.4 A working group of various organisations including representatives from local authorities, veterinary associations and the pet industry developed revised guidance and model conditions based on the original work of the Chartered Institute of Animal Health. The revised documents were to improve interpretation and consistent application of the legislation providing information to both the industry and enforcement officers. The aim of the licence conditions is to ensure high standards of animal health and welfare. Variations to the model conditions are possible, but local authorities should ensure that the principal objectives are met.
- 36.5 The Model Licence Conditions and Guidance for Dog Boarding Establishments recommend that the owners of any animal admitted to kennels must provide proof of current vaccinations for canine distemper, infectious canine hepatitis (ICH), leptospirosis (*L. canicola* and *L. icterohaemorrhagiae*) and canine parvovirus and other relevant diseases. The course of vaccination must have been completed at least four weeks before the first date of boarding or in accordance with the manufacturer's instructions. An additional note advises that vaccination against Kennel Cough should be encouraged and advice sought from a veterinary surgeon given the multi-factorial nature of this disease.
- 36.6 These requirements may be changed at the discretion of the Local Authority. However, this would only be initiated where there is a persuasive argument for changing the requirements e.g. on the basis of new veterinary advice. If there was general consensus from all involved bodies and expert groups on an updated position on vaccination, the Local Authorities Coordinators of Regulatory Services (LACORS), the local government central body responsible for overseeing local authority and related services in the UK, could co-ordinate a revision of the existing Model Licence and Guidance Notes.

37. Promotion of vaccines and National Vaccine month

- 37.1 The VMD does not facilitate or promote any pharmaceutical company's campaign on national vaccination of pets. The VMD regulates the authorisation and supply of veterinary medicinal products and there are very specific controls on certain legal categories of products. All vaccines for dogs are prescription only medicines with a legal category POM-V. A veterinary medicinal product that has been classified as a POM-V may only be supplied once it has been prescribed by a veterinary surgeon following a clinical assessment of an animal or group of animals under the veterinary surgeon's care. Further information on legal categories of veterinary medicines can be found in the Veterinary Medicines Guidance Note 3 <http://www.vmd.gov.uk/General/VMR/vmgn/VMGNote03.pdf>.
- 37.2 This Guidance Note also includes restrictions on advertising POM-V medicines:
- (i) Advertisements for POM-V products may only feature in publications aimed at veterinary surgeons, pharmacists, veterinary nurses and professional keepers of animals. It is not acceptable to promote specific POM-V products directly to members of the public.
 - (ii) Advertising information aimed at the general public may not include the brand name of a POM-V product in relation to treatment but it may name active substances and contain a small strapline at the top or bottom of the article stating 'this information was provided by [company] makers of [product].
 - (iii) The displaying of a poster for a specific POM-V product in a public place e.g. a veterinary

surgeon's waiting room or a shop wall, would be considered as advertising material aimed at the general public and is, therefore, illegal. However, information/educational material that does not contravene the points raised above would be acceptable.

- 37.3 Vaccination reminder cards produced by the manufacturer of a specific product(s) are permitted in certain circumstances. It is acceptable to send a complimentary vaccination reminder card to a client which features a company 'strapline' i.e. 'Brought to you by (company name), makers of (product brand name)'. Any document that features information about a single product is deemed to be advertising. The VMD is not aware of any promotion of the national campaign that has promoted the vaccination of pet animals in an inappropriate way.

Summary

1. The VMD recognises the continuing interest within the veterinary and general pet owning community on the frequency of vaccination and the level of protection afforded by vaccines for companion animals. There is increasing scientific evidence that modified live vaccines (MLVs) for the core-diseases as defined in the WSAVA Guidelines, canine distemper (CDV), canine parvovirus (CPV) and canine adenovirus (CAV) may provide a longer duration of immunity than currently indicated on the SPCs of authorised products. The VMD will continue to work within a regulatory and scientific framework to ensure that re-vaccination intervals are supported by robust data.
2. For the majority of UK authorised dog vaccines the re-vaccination interval for the core vaccines canine distemper (CDV), canine parvovirus (CPV) and canine adenovirus (CAV) is at least every three years. These authorised re-vaccination schedules are in accord with the WSAVA Guidelines which state “not more often than every three years”.
3. The VMD sees no conflict between the APVMA position and that of the UK and other EU regulatory Agencies. The APVMA recognises that in most cases core vaccines need not be administered any more frequently than triennially and that even less frequent vaccination may be considered appropriate. For most UK MLV vaccines for dogs, authorised re-vaccination intervals are at least three years.
4. The duration of immunity of some vaccines is relatively short, with re-vaccination schedules of one year or even less. Annual vaccination with some vaccines may, therefore, be required where a particular animal is at risk of infection. For leptospirosis, a serious endemic disease in dogs and a zoonosis, annual vaccination may be recommended by most veterinary surgeons to ensure an adequate level of protection is maintained. Leptospirosis has a number of wildlife reservoirs and is a particular risk to animals and humans exposed to water contaminated with rat urine.
5. The VMD will continue to seek to develop incentives to promote submission of scientific data to support extended DOIs for core-canine vaccines where this is ethical and proportionate to animal health and welfare. The VMD recognises the financial, logistical and ethical constraints for conducting long-term laboratory studies in small groups of animals to substantiate DOI claims. The VMD will actively promote the recognition of published scientific data to support the revision of vaccination schedules where appropriate.
6. Within the current EU Regulatory framework, each veterinary vaccine is treated as a unique biological product with specific characteristics that determine the profile for safety and efficacy. Each new application for authorisation must be accompanied by an extensive data package containing specific information relating to quality, safety and efficacy for the specific product.
7. The VMD recognises and supports the concerns of the pet owning community and their desire to understand the potential risks to their pets from unnecessary vaccination. In response to these concerns, the Veterinary Products Committee (VPC) established an independent working group on feline and canine vaccination. The full report is available on the VPC’s website <http://www.vpc.gov.uk/Working/feline.html> . The working group concluded in 2002 that vaccination plays a very valuable role in the prevention and control of the major infections in dogs and cats and, although, adverse reactions occasionally occur, the risk/benefit analysis strongly supports their continued use. The VMD is not aware of any new developments that would affect the previous conclusions of the Working Group.
8. It is acknowledged that Pharmacovigilance has a number of limitations that will not adequately address all the issues of adverse events. More information is needed on the prevalence of canine

diseases in the UK to enable veterinary surgeons and their clients to make meaningful benefit/risk assessments on whether to vaccinate an individual animal or not.

9. A veterinary surgeon is empowered to make a clinical benefit/risk judgement based on the local reports of infection and taking account of the age, health, home environment, travel plans and lifestyle for each individual animal presented for vaccination and discuss recommended vaccine schedules with the owner. Thus the decision to vaccinate the individual patient and the frequency thereof is a matter for the veterinary surgeon and his client to discuss. It is not an issue where the VMD should intervene.

10. The VMD will seek to work with BSAVA to provide additional guidance on the authorisation process and the application of the “cascade” to ensure puppies and older dogs receive the most appropriate vaccination schedule for their particular circumstances. This will help to base the decision on whether to vaccinate on an informed benefit/risk discussion between the veterinary surgeon and the owner. Ultimately it is the pet owner who makes the decision to vaccinate.

11. The VMD does not regulate the vaccination requirements laid down by animal boarding establishments. Local Authorities issue licences to proprietors of boarding kennels and catteries under the provisions of the Animal Boarding Establishment Act 1963. Published guidance and model licence conditions have been developed to ensure animal health and welfare. The VMD has no authority or responsibility for the legal and regulatory requirements for boarding establishments.

Veterinary Medicines Directorate

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Glossary

Adjuvant. A vaccine substance administered with an antigen that enhances the immunological response of the animal.

Antigen. The active substance of a vaccine that stimulates an immune reaction in an animal and binds to an antibody or immune cell.

Attenuated vaccine. A vaccine that contains a live microorganism with reduced virulence for the species of animal to be vaccinated. The microorganism is attenuated using a number of techniques that enable the vaccine to stimulate a protective immune response in the animal without causing overt signs of disease.

Blue eye. An immune-mediated reaction in the eye of dogs that may occur following infection with CAV-1 (ICH), rarely with vaccination with CAV-1 and extremely rarely following administration of CAV-2 vaccines. Antibody induced by the vaccine combines with antigen from the vaccine or disease organism to form immune-complexes. The immune-complexes in the eye cause inflammation and swelling which result in a blue discolouration.

Challenge study. A laboratory study in which vaccinated animals and control animals are infected with the virulent disease organism to demonstrate the level of protection afforded by the immune response induced by the vaccine. Vaccinated animals may be protected from infection, clinical signs or death, whilst the control animals should show signs of disease.

Endemic (enzootic) disease. A disease that is continuously present in a particular population. Endemic is often used with reference to human disease and is a more commonly used term than enzootic that refers to disease in animal populations.

Epizootic (epidemic). A disease spreading rapidly and extensively in an unusually high number of animals (epizootic) or humans (epidemic) in a particular geographical area or region.

European Medicines Agency (EMA) formerly the EMEA. The European Medicines Agency is a decentralised body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The Agency is responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products (centralised procedure). Under the centralised procedure, companies submit a single marketing authorisation application to the Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). <http://www.ema.europa.eu/home.htm>.

European Public Assessment Report (EPAR) reflects the scientific conclusion reached by the Committee for Medicinal Products for Veterinary Use (CVMP) at the end of the centralised evaluation process. The legal basis for its creation and availability is contained in Article 38(3) of Regulation (EC) No 726/2004. It is made available by the EMA for information to the public after deletion of commercially confidential information. The EPAR provides a summary of the grounds for the CVMP opinion in favour of granting a marketing authorisation for a specific medicinal product. It results from the Committee's review of the documentation submitted by the applicant and from subsequent discussions held during CVMP meetings. The EPAR is updated throughout the authorisation period as changes to the original terms and conditions of the authorisation (e.g. variations, pharmacovigilance issues, specific obligations) are made. EPARs also contain a summary written in a manner that is understandable to the public. <http://www.ema.europa.eu/htms/vet/epar/eparintro.htm>.

Immunogenicity. The ability of a vaccine to stimulate an immune response in an animal. Immunogenicity studies demonstrate the ability of a vaccine to protect an animal against challenge with the virulent disease microorganism.

Inactivated or killed vaccine is a live pathogenic vaccine organism or toxin treated with physical or chemical agents so that it is no longer infectious or toxic to the vaccinated animal. Inactivated vaccine organisms cannot replicate in the animal. Many inactivated vaccines contain an adjuvant (an agent to enhance the immune response) in order to achieve an acceptable level of immunity.

Marketing Authorisation. The UK Veterinary Medicines Regulations require that any person who places a veterinary medicinal product on the UK market does so in accordance with a Marketing Authorisation granted by the Secretary of State or by the European Medicines Agency, subject to certain specific exemptions (for further information <http://www.vmd.gov.uk/General/VMR/vmgn/VMGNote01.pdf>). For a Marketing Authorisation to be granted, an applicant must submit a scientific data package containing quality, safety and efficacy information and studies in accordance with the requirements of the Directive 2004/28/EC amending 2001/82/EC and Technical Annex 20009/9/EC. An authorised product will have an authorisation number, preceded by the symbol **Vm**, on its product literature, e.g. labels; this offers users a clear guarantee that the medicine has been assessed and approved in accordance with the instructions on the product literature. Please note, products authorised via the centralised route will not have a Vm number on their product literature.

Modified Live Virus (MLV) vaccine. A live vaccine prepared from attenuated (reduced virulence for producing clinical signs in the vaccinated animal) pathogenic strains to protect against challenge with the fully virulent wild-type organism.

Mucosal immunity. Immunity provided at the surface membranes that provides protection from infection with virulent microorganisms.

Multivalent vaccine is a combination of several vaccine organisms or antigens in a single formulation. The advantage of multivalent vaccine is a single administration to the animal which will lead to protection against a number of diseases.

Peracute. A very rapid and severe form of a disease.

Potency. A quality measurement of the immunological activity of a batch of vaccine to protect vaccinated animals against challenge with the disease organism or induce an immune response.

Recombinant vaccine. A vaccine antigen or active part of the vaccine that is expressed in another microorganism such as a bacteria, virus or yeast cell. Some recent recombinant vaccines include

antigens incorporated into harmless virus vectors. Recombinant vaccines may be live or killed vaccines and contain only a small part of the infectious agent, therefore eliminating the risk of the vaccine reverting to virulence. Live recombinant vaccines can stimulate both antibody and cell mediated immunity.

Reversion to virulence. A process in which a live vaccine microorganism regains its virulence in an animal. This may occur after several passages in the species of vaccinated animal.

Serovar is a group of closely related microorganisms distinguished by a characteristic set of antigens.

Sub-unit vaccine. A type of vaccine consisting of specific protein units of the pathogen rather than the whole organism, for example, specific proteins from a virus or bacteria.

Summary of Product Characteristics (SPC). A Summary of Product Characteristics (SPC) contains information about a product that is supported by the scientific data submitted during the application for a Marketing Authorisation.

For example, the SPC gives:

- the name, potency/antigen content and pharmaceutical form of the product.
- the name and potency/antigen content of each active substance.
- the animal species it can be administered to.
- the level of protection against infection, clinical signs or mortality.
- the shelf life..

It also gives safety warnings, which may include:

- warnings about the product's use, for both the person administering the product and for the animal(s) the product is being administered to. Mineral Oil adjuvanted vaccines are a particular risk if a self-injection injury is inflicted on the person administering the vaccine.
- warnings about the product's use in various categories of animals such as pregnant animals or in very young animals.
- information about the safe disposal of the product and its packaging, to ensure safety to protect the environment.

The SPC forms part of a product's MA and it cannot be changed without prior approval from the VMD. Some products also have datasheets, which are different to the SPC. The VMD does not assess or approve datasheets because they are not a requirement under legislation, however, the information in the datasheet should be the same as the information contained in the approved SPC.

Electronic versions of authorised SPCs (known as eSPCs) are available on the VMD's website by clicking on the "+" next to the product name on the VMD's product information database on the VMD website

UKPAR is a United Kingdom Public Assessment Report. All products authorised after 30 October 2005 have an UKPAR in accordance with legislation, which can be found by clicking on the "+" next to the product name on the VMD's product information database on the VMD website. An UKPAR is split into three parts:

1. Summary of Product Characteristics (SPC).
2. Scientific Discussion: a summary of the assessment report drafted during the application procedure covering quality, safety, environmental safety and efficacy.
3. Post Authorisation Assessments: this sets out any changes that have been made to the MA since it was first authorised, e.g. any variations or renewals conducted on an MA.

Veterinary Products Committee is an independent scientific committee under the Veterinary Medicines Regulations to give scientific advice on any aspect of veterinary medicinal products asked for by the Secretary of State

(http://www.opsi.gov.uk/si/si2009/uksi_20092297_en_1)

Virulence. The ability of a microorganism to produce disease in the affected animal.

X-CICADA-Live is a Computer-based Investigation into Companion Animal Disease Awareness. The research data was collected in the six months to May 2009 by Intervet/Schering Plough Animal Health. The response compiled from 95 veterinary practices (representing 332 vets) across Britain and includes suspected and confirmed incidents of disease.

Zoonosis. A disease of animals that is transmissible to man.