

**AMTRA MARKETING AUTHORISATION HOLDERS  
REPRESENTATIVES TRAINING MANUAL  
(2007 EDITION)**

**FOUNDATION COURSE**

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# **AMTRA MARKETING AUTHORISATION HOLDERS REPRESENTATIVES TRAINING MANUAL**

## **Introduction and specimen papers**

### **Introduction**

Animal medicines are vital for the care of domestic animals, whether on the farm or in the home. At the same time they are potent materials which need treating with respect if they are to be used to best effect and without harm to the animal patient, user, consumer or environment. In recognition of this fact, Governments around the world have developed a series of laws, codes and guidelines to control their sale, supply and use.

Medicinal products, and the complex laws which surround them, require properly trained personnel to handle them at every stage in the supply chain. Manufacturing and wholesale premises are inspected and licensed, merchants' and saddlers' and pharmacy premises must be registered with the Royal Pharmaceutical Society of Great Britain (RPSGB) or the Department of Health and Social Security in Northern Ireland (DHSS(NI)) and staffed by qualified personnel, holding the Animal Medicines Training and Regulatory Authority (AMTRA) Certificate, and of course veterinary surgeons and pharmacists have strict professional requirements of education and ethical conduct.

Since 1974 the Codes of Practice of first the Association of the British Pharmaceutical Industry (ABPI) and then National Office for Animal Health (NOAH) have required the sales staff of animal medicine manufacturers to be trained, but until 1992 that training has not been defined, nor has there been any specific qualification.. In 1989 the Board of NOAH recognised this anomaly and created a Training Committee to devise a scheme of training and qualifications.

The Committee recognised the vital role of the manufacturer's representative in transmitting knowledge about the products themselves, the law and codes which control their use and indeed the basic principles of animal physiology and animal husbandry and care. It is also recognised that any qualification awarded should be independent of the industry itself and capable of commanding the respect of those who sell and use animal medicines, as well as the public at large.

This Foundation Syllabus and course notes are the result of those deliberations. Candidates who pass the examination will have demonstrated that they have a solid foundation of knowledge with which to support their work, assist and advise their customers. The Examination, set and supervised by AMTRA, will be a truly independent assessment of their abilities. AMTRA itself is recognised by the Department for the Environment, Food and Rural Affairs (DEFRA) who appoints two of its directors; and observers from the Veterinary Medicines Directorate (VMD) attend its meetings.

Those who pass the examination will hold a unique qualification, specifically designed to support them in their key role, their knowledge and understanding will make them ambassadors for the industry - we wish them well.

# 1. Animal Health Industry

On completion of this section you should:

1. Have an awareness of the major legislation that may affect you and your customers.
2. Be aware of the way in which animal medicines are developed, registered and finally labelled for specific legitimate use.
3. Be familiar with the industry's Code of Practice for the promotion of animal medicines.
4. Be aware that legislation and the Code of Practice are liable to change. This is one area where you have a continuing responsibility to keep up to date.

## 1.1 Overview

### *Interdependence of humans and animals*

Since the start of domestication of animals by man, there has existed an interdependence between man and his animals. The breeding and rearing of animals has now many more purposes than the original provision of food in the form of meat, milk, skins and hides. Animals are now used for work by the police, the military and security organisations (guard duties, drug and explosive detection) and on farms for herding livestock, for companionship (pets, guide and hearing aid dogs), for sport and recreation (greyhound racing, game retrieval, racing, eventing and livery), and in medical research.

As a result, man has realised that in order to maximise the benefit of this relationship the needs of the animals under his care need to be met. The provision of food of the correct quality and quantity and the conditions under which the animals are maintained (shelter, space and the allowance for the expression of behavioural needs) all come into the equation.

Last, but by no means least, the maintenance of animals in a healthy state is desirable. Ideally, the prevention of disease is the goal but if this cannot be achieved then the effective treatment of animal disease is required. Not only are the productivity and profitability of a sick animal less than that of a healthy one, but certain diseases have the capacity to affect both man and animals. These are known as zoonoses. For all of the above reasons the Animal Health Industry has developed in its many forms and these will be described in more detail later in this chapter.

### *Food chain animals*

The term food chain is used to describe those animals which are kept to provide food for the human population. The most numerous of these animals are cattle, sheep, pigs and poultry. Other animals such as deer, goats, fish, honey bees, rabbits and horses may be added to this list.

<b>Numbers of food chain animals in UK</b>	
Cattle	10.3m
Sheep	35.3m
Pigs	4.8m
Poultry (Egg production)	38m
Poultry (Broilers)	120m
Turkeys	7m

Defra 2005

The importance of this group with regards to veterinary medicines is that any residue, in the meat or any other edible part of the animal, or in its produce (milk, eggs, honey) of any medicine used must be below a certain critical level. This is to ensure that people consuming these products do not unwittingly consume material which may harm them or affect the efficiency of any human medicinal products which may be prescribed for them. To achieve this end a set period of time must elapse between the administration of a medicine and the slaughter of the animal or consumption of its produce. This is known as the withdrawal period.

Should residues be found in the tissue or produce of an animal intended for human consumption then an investigation is carried out to determine the cause of the residue. The farm of origin of the animal is visited. Farmers are obliged by law to record all medicinal treatments which have been given to their animals, usually in the form of a “Medicines Book”. An inspection of these records is carried out to determine if, when and how the animal was treated.

### ***Non food animals***

This term refers to all the animals which are not used for human consumption.

The list includes dogs, cats, horses, rabbits, ornamental birds and fish. There is some ambiguity in this list as the rabbits included here are pet rabbits, not wild rabbits or those bred for human consumption, and the inclusion of horses requires a declaration by the horse owner that their animal is not intended for human consumption.

<b>Numbers of non food chain animals in UK</b>	
Dogs	6.8m
Cats	7.5m
Rabbits	1.5m
Horses	1m

As these animals are not in the human food chain there is no requirement for a withdrawal period to be observed or the treatment recorded.

## ***1.2 Regulatory Bodies & Associations***

Taking an overview of the Animal Health Industry it can be seen that it can be divided into several sectors. These are described as follows:

### ***The Veterinary Pharmaceutical Industry***

These are the companies which carry out the research and development of veterinary medicines. This work can take many years and in addition the companies have to satisfy the requirements of the regulators (Veterinary Medicines Directorate (VMD) or European Medicines Agency (EMA)) concerning the safety, quality and efficacy of their product before it can be authorised for sale.

### ***Veterinary Surgeons, Pharmacists, Agricultural Merchants, Saddlers and Pet Care retailers***

These are the people to whom veterinary medicines are sold by the Pharmaceutical Industry and who, by virtue of their training, are permitted to sell these products to animal owners. The professional conduct of Veterinary Surgeons and Pharmacists is controlled respectively by the Royal College of Veterinary Surgeons (RCVS) and the Royal Pharmaceutical Society of Great Britain (RPSGB) or the Pharmaceutical Society of Northern Ireland. A Code of Practice for the Registration of Retail Premises and Suitably Qualified Persons (SQPs) has been issued by the VMD under the Veterinary Medicine Regulations, which will be reviewed and where necessary revised each year, and this governs the conduct of SQPs. The Animal Medicines Training Regulatory Authority (AMTRA) has been appointed by the Secretary of State to ensure SQPs meet their professional obligations.

### **Regulatory Bodies**

#### ***Veterinary Medicines Directorate (VMD)***

The Veterinary Medicines Directorate (VMD) is an Executive Agency of the Department for Environment, Food and Rural Affairs (Defra). Its main aim is to protect public health, animal health and promote animal welfare by ensuring the safety, quality and efficacy of all aspects of veterinary medicines in the UK.

The VMD is responsible for the assessment, issue and maintenance of all national marketing authorisations for veterinary medicines in accordance with European and domestic legislation.

The VMD is also responsible for controls on the manufacture and distribution of veterinary medicinal products, and the surveillance for residues of veterinary medicines in animals and animal products. It also provides policy advice to Ministers on matters relating to veterinary medicines.

### ***State Veterinary Service (SVS)***

The State Veterinary Service (SVS) is a GB-wide organisation dealing with animal health, public health, animal welfare and international trade. Operating a network of veterinary, technical and administrative staff, the SVS carries out a range of responsibilities, many of a statutory nature, including:

- dealing with outbreaks of notifiable diseases;
- carrying out welfare visits to farms and markets;
- advising farmers on disease prevention and requirements for importing and exporting;
- taking samples from animals for detecting residues of veterinary medicines;
- approving bulls and boars for use in artificial insemination;
- enforcing legislation in all these areas; and
- training, appointing and directing the work of 7,000 Local Veterinary Inspectors who work as agents in delivering a wide range of tasks, including testing of cattle for TB, and export certification of animals and animal products.

SVS staff liaise with farmers, local authorities, private veterinary surgeons, market operators, transporters, slaughterhouses and many other groups, as well as the general public.

### ***The Animal Medicines Inspectorate***

The responsibility for the registration of retail premises lies with the Animal Medicines Inspectorate (AMI) which is now integrated within the VMD.

The address of the VMD Animal Medicines Inspectorate is:

Animal Medicines Inspectorate  
Stoneleigh Park  
Warwickshire  
CV8 2LZ  
Tel 024 7684 9260

In Northern Ireland these functions are the responsibility of the Department of Health, Social Services & Public Safety (DHSS&PS). Their address is:

DHSS & PS,  
Health Protection Team,  
Room C4.22,  
Castle Buildings,  
Stormont  
Belfast  
BT4 3SQ  
Tel: 028 9052 2118

## **Associations**

### ***The Animal Medicines Training Regulatory Authority (AMTRA)***

AMTRA is the only body recognised by the Secretary of State to maintain a Register of SQPs.

The functions of AMTRA are:

- (a) To maintain a Register of SQPs;
- (b) To ensure that those applying for registration as SQPs have sufficient training to act as SQPs under the Regulations;
- (c) To have in place adequate standards in deciding whether or not to register a persons as an SQP;
- (d) To maintain a programme of CPD;
- (e) To require that all its SQPs observe the VMD Code of Practice.

### ***The Suitably Qualified Person (SQP)***

It is a requirement under the Code of Practice for the Registration of Retail Premises and Suitably Qualified Persons that all persons, except qualified pharmacists and veterinary surgeons, must have undertaken an agreed programme of study and succeeded in an examination provided by a VMD-recognised organisation, e.g. AMTRA, before being eligible for inclusion on the AMTRA Register of Suitably Qualified Persons (SQP). Only persons included on the Register can authorise the sale or supply of authorised animal medicines from registered premises.

An SQP may only supply medicines other than those classified POM-V, and only those that fall within the scope of their own qualification and therefore registration they have obtained. These are separated as follows:

- All animals
- Food producing animals
- Equines
- Companion animals
- A specific species other than the above

There are no formal qualifications required before enrolling with AMTRA as a student SQP. There is an AMTRA examination for each module. The academic standards of the examinations are set by Harper Adams University College, who also mark the examination papers. Each student must have a viva with an AMTRA assessor to determine that they are fit and proper persons to be admitted to the AMTRA SQP Register on succeeding in the written examinations.

### ***The National Office of Animal Health (NOAH)***

This organisation represents the UK animal medicine industry whose aim is to provide safe, effective, quality medicines for the treatment and welfare of all animals. It is the task of NOAH to promote and defend the responsible manufacture, sale, distribution, handling and use of animal medicines and animal health products, and to act as a consultative body to the industry, Government (particularly VMD), the media and the

general public. NOAH also represents the views and interests of its members and informs the outside world about the valuable work of the animal health industry, an industry which plays a key part in farm and companion animal welfare, consumer safety, farm prosperity, environmental protection and scientific innovation.

NOAH's member companies range from large multi-national organisations, which operate around the world, to small independent UK companies. However, due to the structure of NOAH, every member can make its opinion heard so NOAH is the true voice of the industry.

As a member of both IFAH-Europe, the European body representing animal medicine manufacturers, and IFAH, the world-wide body, NOAH is able to pass UK industry information and viewpoints for consideration at the international level, and also channel relevant legislative and technical information back to the UK industry.

NOAH promotes self-regulation by the animal health industry in matters relating to product promotion. The **Code of Practice for the Promotion of Animal Medicines** was developed to ensure ethical standards are upheld when manufacturers market their products. Its purpose is to ensure that marketing information is fair, accurate and objective.

The scope of the Code includes all marketing activities under the control of the participating company, which do or may encourage the prescribing supply or use of the company's products. It includes, for example, the activities of representatives; various aspects of sales promotion such as journal and direct mail advertising including 'teaser' campaigns; the use of films and other audio-visual material and exhibitions; the provision of samples, gifts and hospitality; and responses to technical enquiries if such responses do or may encourage the prescribing supply or use of the company's products.

As well as protecting the image of the industry as a whole, the Code helps to ensure that industry can continue to self-regulate rather than have imposed on it the complex web of legal controls that apply to human medicine promotion. The UK is unusual compared to many other EU member states in the freedoms granted to advertise animal medicines, and effective and strong self-regulation helps to maintain those freedoms. It is therefore essential that all company representatives thoroughly understand the NOAH Code and their responsibilities under the Code.

The Code is upheld by a NOAH Code of Practice committee, which is chaired by an independent practising barrister, has an independent secretary and includes representatives from both the farming and veterinary professions. The code is regularly reviewed and updated and incorporates the European Industry Code of Practice.

NOAH also requires through the Code that its member companies' representatives are qualified through AMTRA (the Animal Medicines Training Regulatory Authority). This helps to ensure that marketing of animal medicines in the UK is undertaken in a responsible manner.

The Code is regularly updated, reaching its 17th edition in July 2006, and representatives should keep up to date with the changes in the Code.

As well as this, NOAH publishes the **Compendium of Data Sheets for Animal Medicines**. This compendium details information relating to many animal medicines.

***Animal Health Distributors Association (UK) Ltd (AHDA)***

AHDA is an association of responsible animal health product distributors, dedicated to serving the best interests of its members, in particular by protecting their rights to sell and supply, and securing the continued availability of a wide range of animal medicines that do not require a prescription from a veterinary surgeon.

The Association also strives to secure the continued availability of such medicines for its members by constant negotiation with manufacturers, government and the European Union.

***The British Equestrian Trade Association (BETA)***

BETA is the body which represents the equestrian manufacturing, wholesale and retail trade in discussions with government and the leading riding organisations. It has created codes of conduct for retailers and suppliers, a Code and Guidelines for suppliers of equine feeds and supplements, developed an internationally recognised trade exhibition (BETA INTERNATIONAL), and runs training courses.

***The Pet Care Trust (PCT)***

The Pet Care Trust is a national charity that promotes the benefits of responsible pet ownership and pet care education and training. The Trust has around 1,400 members, overwhelmingly small and medium enterprises including pet shops, groomers, kennels, catteries, manufacturers, wholesalers and colleges.

Committed to animal welfare over many years, the Pet Care Trust has developed charters representing best practice for the different sectors of the pet trade. These include the Pet Care Charter, a code of conduct which is the foundation for the Government's Model Licence Conditions.

Progressive and pro-active, the Pet Care Trust works continuously to improve the standards of pet keeping by promoting responsible pet ownership, at the same time raising awareness of the benefits of keeping pets, through an ongoing and extensive information programme.

### ***1.3 Legislation and Regulation***

Up until the end of October 2005 the legislation covering all aspects of veterinary medicines was the Medicines Act 1968 and many subsequent Statutory Instruments. On 30 October 2005 the law was consolidated into the Veterinary Medicines Regulations 2005. Replacement Regulations followed for October 2006, and it is anticipated they will be revised and renewed each year.

In these Regulations can be found many things relating to veterinary medicinal products such as the definition of a veterinary medicinal product, and the conditions affecting the manufacture, marketing, importing, advertising, wholesale dealing, retailing, prescribing and the administration of veterinary medicinal products and feedingstuffs. In addition the requirements for keeping of records, controls on unauthorised veterinary medicinal products, and the role of Inspectors and their powers are defined.

#### ***Distribution Categories***

Each authorised veterinary medicinal product is granted a specific distribution category when it is first authorised. A change to the classification of individual medicines within these categories may be made from time to time.

The distribution categories from October 2005 are:

#### **Prescription Only Medicine – Veterinarian (abbreviated to POM-V)**

Prescribed by a veterinary surgeon and supplied by a veterinary surgeon or a pharmacist. (previously POM, MFS and some P products)

#### **Prescription Only Medicine – Veterinarian, Pharmacist, Suitably Qualified Person (abbreviated to POM-VPS)**

Prescribed by one of the Registered Qualified Persons and supplied by one of them (previously PML, MFSX and some P products)

#### **Non-Food Animal – Veterinarian, Pharmacist, Suitably Qualified Person (abbreviated to NFA-VPS)**

Supplied by one of the Registered Qualified Persons (previously PML and some P products)

#### **Authorised Veterinary Medicine – General Sales List (abbreviated to AVM-GSL)**

Supplied by any retailer (previously GSL products)

For AVM-GSL products there is no legislative requirement for prescription or supply and these products may therefore be supplied on request.

#### ***Registered Qualified Persons***

#### **There are 3 different types of Registered Qualified Persons (RQP):**

- i. a **veterinary surgeon** who is registered with the Royal College of Veterinary Surgeons

Manufacturers have until 1 November 2008 to change these categories on packaging and product literature

- ii. a **pharmacist** who is registered with the Royal Pharmaceutical Society of Great Britain or the Pharmaceutical Society of Northern Ireland
- iii. an **SQP** who is registered with one of the bodies approved by the Secretary of State.

It is an offence for any person to supply a veterinary medicinal product within the distribution categories POM-V, POM-VPS or NFA-VPS unless that person is an RQP and supplies the product in accordance with the current Regulations.

### *Suitably Qualified Persons (SQPs)*

To be a suitably qualified person (SQP) it is necessary to have passed examinations set by AMTRA.

AMTRA has a legal obligation to ensure SQPs registered with it abide by the Code of Practice issued by the Secretary of State. Depending upon the degree of change in the annual update of the Regulations, the Code may have to be updated each year. The full text of the current Code of practice can be found on the website of AMTRA – [www.amtra.org.uk](http://www.amtra.org.uk)

An SQP may only supply the medicines that fall within the scope of the qualification and therefore registration they have obtained. These are separated as follows:

- All animals
- Food producing animals
- Equines
- Companion animals
- A specific species other than the above

### *Duties and Responsibilities of SQPs*

It is the duty of an SQP to ensure that the statutory requirements in respect of the prescription and supply of POM-VPS and NFA-VPS medicines are respected. The SQP is responsible for ensuring this irrespective of how the product is supplied.

The options for registration currently provided by AMTRA are detailed below:

R-SQP	FAM + EQM + CAM	All VPS Medicines
G-SQP	FAM + EQM	VPS for farm animals & equines
K-SQP	FAM + CAM	VPS for farm & companion animals
E-SQP	EQM + CAM	VPS for equines & companion animals
L-SQP	FAM	VPS for farm animals only
J-SQP	EQM	VPS for equines only
C-SQP	CAM	VPS for companion animals only

An SQP may not prescribe or supply a product outside the terms of their individual registration.

### ***Prescription***

In order to supply a product authorised as POM-V or POM-VPS, an RQP first has to prescribe the product. The act of prescribing includes the decision made by the SQP as to which product should be supplied.

The 2006 Regulations state (Schedule 3, Part 1 Paragraph 5(1)) that a POM-V or POM-VPS medicine may only be supplied by the person who prescribed it, or under a written prescription.

However, if the medicine is prescribed AND supplied by the same SQP, then a written prescription is not necessary – an oral prescription will suffice. The RQP should be prepared to provide a written prescription on request.

### ***Regulations***

It is an offence under the Regulations to:

- possess an unauthorised veterinary medicinal product except in accordance with the Regulations or for the purposes of research and development;
- supply an unauthorised veterinary medicinal product;
- supply a veterinary medicinal product that has passed its expiry date;
- substitute a different product for a medicine that has been prescribed by another Registered Qualified Person.

### ***Definition of a Medicinal Product***

The Veterinary Medicines Regulations define “veterinary medicinal product” as follows, a definition originally deriving from Directive 65/65:

- (a) any substance or combination of substances presented as having properties for treating or preventing disease in animals; or*
- (b) any substance or combination of substances that may be used in, or administered to, animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

A product falling within the first part of the definition is said to be a medicinal product "**by presentation**", and within the second a medicinal product "**by function**".

Any product falling within either of these definitions must have a UK or EU veterinary medicine Marketing Authorisation if it is to be sold (or possessed or administered) in the UK.

### ***Development of animal medicines***

Before an animal medicine can be sold in the UK it must be approved. This takes the form of a marketing authorisation. The UK has one of the most stringent licensing systems for the authorisation of animal medicines in Europe, if not the world.

Development of a new animal medicine is very lengthy and expensive process. To develop a new product from scratch takes many years and costs millions of pounds.

Once a potentially useful compound has been identified, amongst other things:

- studies have to be done into its pharmacology and modes of action
- studies are carried out into its potential toxicity (both acute and long term: to the animal, the person who will administer the medicine, the consumer of any produce from a treated animal and the environment)
- analytical methods have to be developed to look for any residues left
- dose finding studies are carried out to find out at what dose the substance is effective in the appropriate species
- for farm animal medicines there has to be a Maximum Residue Limit for the active ingredient and residue depletion studies are needed to set withdrawal periods
- production methods have to be devised and scaled up to a commercial production line
- work is done on the formulation of the product
- stability tests are carried out
- field trials are run to test the product in real life

To apply for the marketing authorisation needed to sell an animal medicine, the company has to put together a very extensive dossier of information, which must follow a pre-determined format to set out in European law. This information helps the national or European regulators to carry out an independent scientific assessment of a product's safety, quality and efficacy.

### ***Marketing Authorisations***

Medicines must meet criteria of safety, quality and efficacy before they are authorised and these criteria are laid down in detail in the Annex to EU Directive 2001/82, coupled with many guidelines from the EU's Committee for Veterinary Medicinal Products and other regulatory bodies and committees.

***Safety*** refers to safety to the animal, to the environment, to users of veterinary medicines and, from food animal species, to the consumer who will eat products of animal origin which may contain residues of veterinary medicines.

***Quality*** The quality criterion says of a product that it is manufactured according to specific standards of purity and consistency. These standards apply throughout the production and formulation process. Stability studies ensure that the product retains its full potency, efficacy and safety, even when stored for long periods.

***Efficacy*** "Efficacy" means that the customer can be assured that the product will do what is claimed for it. When used as directed (i.e. correct dose rate, frequency and duration of treatment), it will be effective in the circumstances set out on the label. To support this claim, a product is tested extensively in the laboratory, in disease challenge studies and finally in field trials, which must demonstrate that it works under conditions of practical field use.

<p>Safety Quality Efficacy</p>
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There are four routes for obtaining marketing authorisations:

- the National procedure under which applications with supporting data are submitted to the Veterinary Medicines Directorate (VMD), an executive agency of the Department for Environment, Food & Rural Affairs. Marketing authorisations granted under this procedure are valid in the UK only. Only products that are not already authorised anywhere in the EU are eligible for the national procedure.
- the Decentralised and Mutual Recognition procedures are very similar: a holder of a marketing authorisation issued by one member state may apply to one or more other member states to issue identical authorisations on the basis of “mutual recognition”. If a product is not yet authorised anywhere in the EU, an application may be made simultaneously to several member states under the Decentralised Procedure, with one of the member states (the “rapporteur”) taking the lead on assessment of the dossier.

If one of the member states concerned considers that the product as authorised constitutes a risk to animal or public health or to the environment, the dossier is first referred to a coordination group called CMD(V) in an attempt to reach agreement. If that fails, it is referred to the EU Committee for Veterinary Medicinal Products (CVMP) for “arbitration”, where a binding decision is reached.

- the Centralised procedure is obligatory for some high technology products and optional for some other products. An application is made to the European Medicines Agency (EMA). The marketing authorisation, if subsequently granted, is issued by the European Commission and is valid in all member states.

### ***Maximum Residue Limits***

A key tool for the protection of consumer health for animal medicines used in food species is the **maximum residue limit (MRL)**. The MRL is the maximum concentration of residue resulting from administration of a veterinary medicinal product which is legally permitted in the EU or recognised as acceptable in or on food. MRLs are established by the European Commission through the Committee for Veterinary Medicinal Products (CVMP) and its Working Group on the Safety of Residues in conjunction with the European Medicines Agency (EMA). In addition to serving as safe limits, MRLs also serve other related purposes. From the consumer safety view point, they form the basis for establishing withdrawal periods.

MRL
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Moreover, they also form the basis for residues surveillance serving as regulatory limits and finally, their establishment at EU and international level should serve to remove barriers to international trade in both animal produce and veterinary medicines.

### ***The basis for MRLs***

Two concepts lie behind the establishment of MRLs for veterinary medicines – the **no-observed effect level (NOEL)** and the **acceptable daily intake (ADI)**.

The NOEL is usually taken as the dose from toxicological studies, or, for antibiotics, from microbiological studies, below which adverse effects do not occur. It is usually determined in the most sensitive species for the most sensitive effect.

The ADI is calculated by dividing the NOEL by a suitable **safety factor (SF)** which is usually 100 (x10 for animal-human variation and x10 for human-human variation) but its value can be greater depending on the type of effect and the quality of data package. Occasionally, it may be smaller (usually 10) if the NOEL is based on effects in humans.

Products for food producing animals need an MRL

Thus, 
$$\text{ADI} = \frac{\text{NOEL}}{\text{SF (100)}} \text{ mg/kg body weight}$$

If this is multiplied by the widely accepted 'standard' adult weight of 60kg:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF (100)}} \times 60 \text{ kg}$$

then the value is derived in terms of mg per day per person.

The result of the implementation of this system is that extremely small residues are permitted to enter human food as they are considered to pose no risk to human health.

Examples of MRLs are shown in the table below

Drug	Tissue	
	Muscle	Milk
Fenbendazole	50 µg/kg	10 µg/kg
Flumethrin	10 µg/kg	30 µg/kg

MRLs are measured in µg/kg

### ***Withdrawal periods and surveillance***

One of the major uses of the MRL is in the establishment of the withdrawal period. This is the minimum period between medicine administration and slaughter or the collection of milk or other animal produce for human consumption. In the UK, it is usually set at the time that the marker residue falls below the MRL in the target tissues in all animals in a group from a serial slaughter residues depletion study.

The other major purpose in setting MRLs, as described earlier, is for surveillance purposes. Where no MRL is available, for example where authorised medicines are used illegally, or where prohibited medicines are used, an analogous Action Level is used.

The VMD operates two complementary surveillance programmes. The first, the **National Surveillance Scheme (NSS)**, implements EU legislation, and a non-statutory programme which supplements and expands the statutory programme.

The costs of the statutory programme are met by charges levied on the meat industry, while the non-statutory programme is funded by Defra. At the present time the UK examines annually almost 40,000 tissue samples for the violation of MRLs or for the presence of residues of prohibited substances, but the incidence of positive findings is extremely low. The results are published quarterly by the VMD publication “MAVIS” at [www.vmd.gov.uk](http://www.vmd.gov.uk), and annually in the Veterinary Residues Committee’s annual report at [www.vet-residues-committee.gov.uk](http://www.vet-residues-committee.gov.uk)

There are powers in law to remove from the food chain products containing residues at levels which represent a danger to human health. All samples above the MRL or “Action Level” are followed up and may result in a prosecution.

Withdrawal periods are included on all medicine packaging, and are included in the Compendium of Data Sheets for Animal Medicines available from NOAH or at [www.noahcompendium.co.uk](http://www.noahcompendium.co.uk), and are contained in the product Summary of Product Characteristics (SPC) at [www.vmd.gov.uk](http://www.vmd.gov.uk).

#### ***Record keeping - prescribers***

Those persons permitted to supply POM-V or POM-VPS medicines must keep records of all incoming and outgoing supplies of these medicines, including the date, name and amount of medicine, batch number, name and address of supplier or recipient, and where it is written, a copy of the prescription. These records must be kept for five years.

#### ***Record keeping – farmers***

If food producing animals are kept then it is a legal obligation to keep a record of all medicines purchased or otherwise acquired, administered, or disposed of. This record must be kept available for inspection by authorised persons, most commonly in the form of a Medicines Book, though alternative forms of record-keeping are permitted provided the information needed is readily available.

Records should be kept for five years.

#### ***Recognition of an Authorised Veterinary Medicinal Product***

There are two pieces of information present on the packaging of and authorised veterinary medicinal product which can only be found on these products. These are:

1. The Marketing Authorisation Number. This can take one of two forms:

- 98765/4321, usually preceded by Vm, standing for “veterinary medicine”. The numbers 98765 indicate the marketing authorisation holder and the final numbers 4321 are unique to the product.
- EU/2/06/025/001, where EU/2 indicates this is a veterinary medicine authorised by the European Commission, 06 is the year of first authorisation, 025 is the product number, and 001 is the “subdivision” of the product (e.g. size of tablet, route of administration).

2. The distribution category. These are the letters indicating the category to which the product belongs, i.e. POM-VPS, NFA-VPS or AVM-GSL. (Manufacturers will be permitted to sell products bearing the old designations PML, P, MFSX and GSL until 1 November 2008.)

Additionally, the Regulations permit the inclusion of the words “UK authorised veterinary medicinal product”, or similar, or a logo including those words, but this is not a legal requirement.

### ***Pharmacovigilance – Suspected Adverse Reactions***

Pharmaceutical companies are legally required to keep a record of any information they receive about suspected adverse reactions to their products and to pass on these details to the VMD or EMEA.

A **suspected adverse reaction (SAR)** is a harmful and unintended reaction which may be due to exposure to a veterinary medicine administered to an animal at its normal dose. (In other words any harmful, unexpected side effect to a veterinary medicine.) The scheme monitors reactions both in animals and people who are exposed to the medicine. Adverse reactions in overdose situations are also recorded. The scheme also records reports of the following instances:

- Where a medicine does not work as intended (lack of efficacy)
- Adverse environmental effects
- Problems with residues of veterinary medicines in human food
- Resistance of target organisms to a veterinary medicine.

SARSS protects animals, people and the environment.

Because of this extended scope in addition to classical SARs, this area of monitoring safety post-marketing is better called **pharmacovigilance**.

Exposure can occur when animals are being treated with veterinary medicines such as vaccines, antibiotics, anaesthetics, tick and flea control products or sheep dips. It can also occur in people who are exposed to veterinary medicines (e.g. self-injections, handling recently treated animals).

The scheme covers all species of animals treated with veterinary medicines. These include animals kept on farms, in zoos, pets and other animals such as reptiles, wild birds, fish and bees.

### ***Pharmacovigilance – company responsibilities***

The Veterinary Medicines Regulations require the holder of each marketing authorisation to “have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance”.

The appropriately qualified person is responsible for setting up and operating a system which ensures that all information about any suspected adverse reactions reported to the company is collected and collated at a single point. Records of suspected adverse reactions must by law be kept for at least 5 years. Representatives therefore have a duty to ensure that all pharmacovigilance reports

are recorded in the company system. The majority of reports received by VMD come from companies.

Periodic Safety Update reports should be sent as required by the VMD. Generally, they are required six-monthly for the first 2 years after product authorisation, annually for the subsequent 3 years, and thereafter every 5 years.

This report lists all the suspected adverse reactions reported to the company since the last Periodic Safety Update report. This is set into context by looking at the incidence of reactions, taking account of the number of doses sold. Each Periodic Safety Update report should contain a concise assessment of the evaluation of the current safety of the product.

#### ***Pharmacovigilance reporting by users***

Although anyone can report to the VMD on an adverse reaction to a veterinary medicine that they have experienced or observed, members of the public, veterinary surgeons, farmers, doctors, pharmacists etc. are all encouraged also to report to the manufacturer of the medicine.

Reports to VMD are submitted on a special yellow reporting form (MLA252A), copies of which are available from VMD and in the NOAH Compendium. Harmful unexpected side effects to veterinary medicines are rare but if there is suspicion that one has occurred in an animal, or a person, one should:

1. Contact the veterinary surgeon, if a pet or other animal is affected, so that it can be treated;
2. Contact a doctor for advice/treatment if a person is affected;
3. Report the reaction to the VMD

#### ***The Suspected Adverse Reaction Surveillance Scheme (SARSS)***

The Suspected Adverse Reaction Surveillance Scheme is a scheme for monitoring reports of suspected adverse reactions to veterinary medicines in both animals and humans throughout the UK, and the other aspects of pharmacovigilance. It is run by the Veterinary Medicines Directorate (VMD).

Every report to the scheme is acknowledged in writing within two working days and its contents are entered on a computerised database. All information in the report, and any information received subsequently, is treated in confidence. Each report is carefully examined to assess:

1. The severity of the reaction;
2. Whether there have been any previous reports to the same or similar products;
3. Whether any further information is required;
4. What follow up action is required.

There is a legal obligation for the scheme to send a copy of the report form to the company whose product is suspected, but the person reporting the side effect has the option to ask for their name and address not to be disclosed.

Sometimes a questionnaire requesting further details/information will be sent to the person reporting the side effect. Where it is a person with a suspected side effect (rather than an animal) they may also be asked for authority for their relevant medical notes to be provided. All medical reports are treated confidentially. Further information may also be sought from the **Health and Safety Executive (HSE)**.

After they have been assessed, all reports of unexpected side-effects in people are reviewed by the **Appraisal Panel for Suspected Adverse Reactions to Veterinary Medicines**. This is a panel of independent experts supported by specialists from the Department of Health, the HSE and the VMD. Its aims are:

1. To evaluate all harmful, unexpected side effects in humans exposed to veterinary medicines;
2. To identify any trends or signs of emerging problems;
3. To report its findings to the Veterinary Products Committee (VPC) (an independent committee of experts which advises government Ministers on the safety, quality and efficacy of veterinary medicines).

There are a number of possible **follow-up actions** that can be taken, including:

1. Monitoring future reports about the product;
2. Recommending that changes are made to the product literature, labels and package inserts, for example to include appropriate warnings;
3. Suspending the sale and supply of the product or of a specific batch of that product;
4. Revoking the marketing authorisation for the product.

In the event of a human or animal SAR occurring the first contact should be a doctor or veterinary surgeon who will be able to discuss the reaction, initiate any treatment required and, where appropriate, report to the scheme. If possible take the medicine container (or label for a large pack) or packaging/insert leaflet.

Reports may be made directly to the VMD using the report form (MLA252A) from the address below.

**It is important that ALL harmful, unexpected side effects to veterinary medicines are reported to the scheme so that appropriate action can be taken to avoid any further harm to animals or people.**

For further information:

The Suspected Adverse Reaction Surveillance Scheme  
Freepost KT4503  
Veterinary Medicines Directorate  
Woodham Lane, Addlestone Surrey KT15 3BR  
Telephone: 01932 338427 Fax: 01932 336618

### ***Summary of the Product Characteristics (SPC)***

The summary of product characteristics (SPC) is a document, approved by VMD or EMEA, which contains information on what a medicine contains (its active

ingredient), what animals it can be given to, what it can be used to treat or prevent and what is its shelf life. It also includes warnings about the product's use with regards to the animal, any hazard it may have for the person administering the medicine and also for the environment if containers are disposed of incorrectly. Withdrawal periods are included to prevent meat, milk or eggs from entering the human food chain until residues have depleted to safe levels.

SPCs for all authorised products are available online at [www.vmd.gov.uk](http://www.vmd.gov.uk), in the Product Information section of the home page and under the heading of eSPCs (electronic SPCs).

### ***Data Sheets***

Prior to the adoption of the European Union requirement that information about a veterinary medicine is presented in the form of an SPC, in the UK this information was provided by means of a data sheet: these are still produced by most companies as a customer service. The data sheets of the majority of companies have been compiled into a compendium which is published annually by NOAH as this serves the valuable function of providing the information in a single volume. This information is now also available online at [www.noahcompendium.co.uk](http://www.noahcompendium.co.uk) and can be searched by manufacturer, species, active ingredient and therapeutic indication.

The information in a data sheet must be not inconsistent with the SPC, but is presented in a slightly different way.

### ***The Prescribing “Cascade”***

The Cascade is a long-standing arrangement providing a rational balance between the legislative requirement for veterinary surgeons to prescribe and use authorised veterinary medicines where they are available, and the need for professional freedom to prescribe other products where they are not. It is intended to increase the range of medicines available for veterinary use.

#### *Why is it important to use authorised medicines?*

Animal species may have many physiological differences from humans and from each other. As a result they each may react differently to medicines. The authorisation system for veterinary medicines requires a product to have proven quality and effectiveness and, most importantly, safety for the animal, the user (vet, farmer, pet owner etc.), the environment and, for food animals, the consumer of animal produce. This assurance has to be provided for each species and each indication on the label.

In addition, animal medicines containing the same active ingredient as human medicines may be formulated differently. For instance, the formulation needs to ensure they are properly absorbed through the gut (which, for example, is rather shorter in a cat than a human). Human medicine formulations may contain different excipients or have different bioavailability from veterinary medicines. Using a

product which is not authorised for animals therefore, increases the risk of harm to the patient.

In addition, the cost of developing a medicine for animal use is high and can involve much research and many tests not carried out for human medicines.

The use of human medicines, in place of the equivalent authorised veterinary medicine, can only be done by referring to the information on medicine use provided by animal medicine companies. Assuming the data is transferable in this way is potentially hazardous and doing so takes advantage of work done by the animal medicine industry without paying for it. This means that those users abiding by the rules are subsidising those who do not, and such abuse diverts essential funding away from future research and development for new veterinary medicines.

It is important to address the potential confusion with the use of the word “generic”. Authorised veterinary generics exist legitimately which can be used by vets as other authorised animal medicines. However, human generic medicines that are similar to the authorised veterinary medicines may not be used unless there is no suitable veterinary medicine available.

The Cascade provides a legal mechanism allowing veterinary surgeons to use their clinical judgement to prescribe a suitable medicine where no authorised medicine exists. Use and prescription by vets of human generic medicines where a suitable veterinary product is available is a criminal offence and contrary to the RCVS Guide to Professional Conduct.

Vets remain entirely responsible for the treatment of animals under their care; use of a medicine under the cascade should be capable of being supported by clear auditable clinical evidence to justify the vet’s decision.

*What do vets need to do to comply with the cascade?*

If there is no medicine authorised in the UK for a specific condition, the Veterinary Medicines Regulations state that the veterinary surgeon responsible for treating the animal(s) may, in order to mitigate unacceptable suffering, treat the animal(s) in accordance with the following sequence:

- (a) a veterinary medicine authorised in the UK for use in another animal species or for a different condition in the same species; or, if there is no such product;
- (b) either:
  - (i) a medicine authorised in the UK for human use, or
  - (ii) in accordance with an import certificate from VMD, a veterinary medicine from another Member State; or, if there is no such product;
- (c) a medicine prepared extemporaneously, by a vet, pharmacist or a person holding an appropriate manufacturer’s authorisation.

If the animal(s) are food-producing animals, then the following additional conditions apply:

- the treatment in any particular case is restricted to animals on a single holding

- any medicine imported from another Member State must be authorised for use in a food-producing species in the other Member State
- the pharmacologically active substances contained in the medicine must have MRLs
- the prescribing vet must specify an appropriate withdrawal period – statutory minimums are in the Regulations
- the prescribing vet must keep specified records.

A medicine prescribed in accordance with the cascade may be administered by the prescribing vet or by a person acting under their direction. Responsibility for the prescription and use of the medicine remains with the prescribing veterinary surgeon.

For further information, please see the VMD's Veterinary Medicines Guidance Note 15, "Controls on the Administration of Veterinary Medicines", available from [www.vmd.gov.uk](http://www.vmd.gov.uk).

### ***The Small Animal Exemption Scheme***

There exists a scheme which permits certain veterinary medicines to be sold for specific categories of pet and other animals without having a Marketing Authorisation and hence a Vm number or a distribution category e.g. POM-VPS etc.

The animal categories are

- Aquarium fish
- Cage birds
- Homing pigeons
- Terrarium animals such as reptiles, amphibians and arthropods kept in tanks and cages. Also animals free living in domestic gardens.
- Small rodents
- Ferrets rabbits

In addition animals kept at rescue centres, animals bred as food for other species, animals kept for laboratory purposes and animals kept for financial gain (sport, exhibition or sale).

Products marketed under this scheme must contain a statement on the label saying "This veterinary medicine is marketed in accordance with the Small Animal Exemption Scheme"

There are limitations on the pack sizes and hence the number of animals which may be treated in a single course and any serious adverse reactions should be reported to the VMD within 15 days.

For further information, please see the VMD's Veterinary Medicines Guidance Note 14, "Marketing Authorisation Exemption Scheme for Pet Animal Medicines", available from [www.vmd.gov.uk](http://www.vmd.gov.uk).