VETERINARY PHARMACOVIGILANCE IN THE UK

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In the United Kingdom, responsibility for the regulation of veterinary medicines lies with the Veterinary Medicines Directorate (VMD), an Executive Agency of the Department for Environment, Food and Rural Affairs (DEFRA). Regulation of human medicines is carried out by a different body, the Medicines and Healthcare products Regulatory Agency (MHRA), an agency of the Department of Health.

The VMD is based in Surrey, approximately 30 miles southwest of London and employs approximately 155 people, from a variety of different scientific disciplines, including veterinary surgeons, pharmacists, chemists, immunologists, toxicologists, ecotoxicologists and epidemiologists, along with administrative staff and those with expertise in the fields of policy making, finance and IT.

Broadly speaking, the VMD has two main divisions;

AUTHORISATIONS

It is responsible for the assessment and processing of all applications for new Marketing Authorisations (MAs) as well as variations to, and renewals of existing MAs, along with approval of clinical trials in the UK. Scientific assessment of these applications is carried out by two different teams: one for immunological products and one for pharmaceuticals and feed additives. It should be noted that whilst the VMD contributes to the assessment of feed additives, these products are ultimately the responsibility of a different authority in the UK, the Food Standards Agency (FSA), who work closely with the European Food Safety Authority (EFSA). Due to the increasing number of novel therapeutics being developed, assessment of some biological products is carried out using expertise from both the pharmaceutical and immunological teams.

OPERATIONS

It encompasses a diverse range of teams responsible for the development of legislation and policy and enforcement of the regulations as well as the **POST AUTHORISATIONS SURVEILLANCE UNIT** with two inspection teams, one responsible for inspecting manufacturing premises (including their pharmacovigilance systems), the other inspects wholesalers, feedmills and veterinary practices. In addition, there are a further three teams responsible for residues surveillance, antimicrobial resistance surveillance and policy formulation and, last but by no means least, pharmacovigilance for veterinary medicines.

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Approximately 80% of funding for the VMD's work comes from industry through fees for MA applications and an annual fee linked to each MA (which pays for pharmacovigilance work along with other costs associated with maintaining an MA), inspection fees and a levy on abattoirs pays for the statutory residues surveillance. The remaining 20% comes from central government, which funds the policy and enforcement work and, for the time being additional, non statutory residues surveillance of food being imported from outside the EU.

The VMD's Pharmacovigilance Unit is relatively small, comprising eight members of staff, including two vets, who are responsible for recording and assessing all spontaneous reports received relating to suspected adverse reactions in animals and humans, suspected lack of expected efficacy (SLEEs), environmental incidents and occasions where residues above the Maximum Residue Limit (MRL) have been detected in food products. In addition to spontaneous reports, the team also records and assesses the information provided by Marketing Authorisation Holders (MAHs) in Periodic Safety Update Reports (PSURs).

Although relatively small, the pharmacovigilance unit is well established, having been set up in 1985, some years before it became a legal requirement for veterinary medicines under the EC Directive 2001/82/EC. However, prior to this, the original *Notice to Applicants* (concerning medicinal products for human use) was first published in 1986, completed in 1989 and updated in 1993, 1994 and 1996. This included a Chapter (V) on pharmacovigilance guidance for MAH and Volume VB of the *Notice to Applicants concerning medicinal products for veterinary use* (III/5056/95, published as a draft dated January 1995) included a Chapter V - Pharmacovigilance. All this guidance (for human and veterinary medicines) was collated into the original Volume 9 of The Rules Governing Medicinal Products in the European Union and finally, in October 2011, Volume 9B was published which relates only to veterinary medicines and is the framework from which we work today.

Over the almost 30 years that the Suspected Adverse Reaction Surveillance Scheme (SARSS) has been running in the UK, over 45,000 individual reports have been recorded in our bespoke IT database, affectionately named TIGRESS, which stands for Totally Integrated Graphical Relational Electronic Surveillance System. Unlike in some other countries, it is not mandatory for vets in the UK to report adverse events and suspected lack of efficacy, however the profession has embraced the scheme very well and report numbers have been increasing year on year, with almost 4300 reports received during 2012. Each year we publish in the Veterinary Record (the UK veterinary profession's weekly journal) an annual report which describes trends seen in suspected adverse reactions and lack of efficacy and this is supplemented throughout the year by letters or articles if particular issues have come to light that the profession needs to be made aware of.

Historically, all our reports were received on paper forms but we have adapted with the times to embrace new technology. It is now the case that serious reports received by MAHs (that by law must be reported to us within 15 days) can be transmitted via

Eudravigilance (a system developed by the European Medicines Agency (EMA), in partnership with EU regulatory authorities and industry) and enters our database directly, with an electronic confirmation sent back automatically to acknowledge receipt.

In addition, since September 2010, we have had the facility for reports to be submitted directly to our database via a portal on our website. This has been a very important step to increasing the reporting of adverse events as it means that anyone (including pet owners, farmers, doctors and other veterinary practice staff in addition to vets) can make a report and receive an electronic acknowledgment immediately.

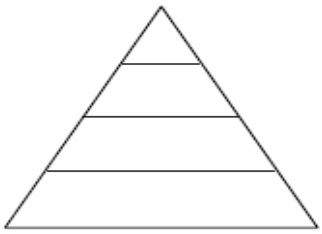
The take up of electronic reporting has been very successful. At the beginning of 2010, paper reports comprised approximately 60% of those received, with Eudravigilance making up the remaining 40%. However, by the end of 2012 only about 25% of reports were received on paper, with online reports via our website making up approximately 15% of the total and in the meantime the proportion received via Eudravigilance has increased to almost 60%. As well as improving the ease with which stakeholders can submit reports to the VMD, which in itself increases reporting, these developments also improve our efficiency in processing them, so we can concentrate resources on analysis of the data, which are becoming ever more useful as the dataset expands.

In recognition of this, since 2009, the VMD has invested considerable resource into promoting the activities of the VMD, including adverse event reporting, by producing a range of leaflets and attending veterinary congresses and public exhibitions such as Crufts (the largest dog show in the UK), the London Pet Show and agricultural events to target the farming community. The reaction to our presence at such events has been overwhelmingly positive and has allowed us to educate, answer questions and provide advice to animal owners and veterinary professionals on how to use veterinary medicines safely and effectively and what to do when problems occur. We are also able to demonstrate to them how to access our website and show them how to search our product information database, apply for import medicines from abroad or report adverse events online.

As veterinary pharmacovigilance has developed and become more established globally, it has become increasingly important that data can be transmitted between regulatory authorities around the world. Within the EU, the UK was instrumental in developing the Veterinary Dictionary for Drug Related Affairs (VEDDRA) which is loosely based on a system developed for use in human pharmacovigilance (MEDDRA).

VEDDRA provides a terminology for recording clinical signs or other easily detectable clinical information. It consists of a four level hierarchical structure:

- LLTs are either a synonym or a sub-classification of a particular PT (eg: walking difficulty)
- PTs represent a single clinical concept (eg: ataxia)
- HLTs are broader terms than the PTs linked to them and provide clinically relevant



SOC = System Organ Class

HLT = Higher Level Term

PT = Preferred Term

LLT = Lower Level Term

groupings (eg: coordination and balance signs)

· SOCs describes the organ or body system affected (eg neurological disorders)

Unlike MEDDRA, this system is mono-axial, so that each LLT is unique and is linked to a single PT which is then only available in one specific SOC. The simplicity of this system was what helped to persuade the FDA to adopt the same terminology for its veterinary pharmacovigilance work, which has been of great benefit to all parties concerned.

Another development in recent years has been the introduction to TIGRESS of another tool to aid in signal detection, which has in the past mostly been based on looking at each report on receipt and performing a case-by-case causality assessment. The long-term analysis of the pharmaco-toxicological profiles of the products therefore depends on the personal experience of each assessor and becomes more difficult as the number of reports received increases.

Automated signal detection is based on a statistical analysis of the adverse event data. Numerous methods are available including the Multi-item Gamma Poisson Shrinker (MGPS), the Bayesian Confidence Propagation Neural Network (BCPNN), the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), the Chisquare test (X^2).

The VMD decided to adopt the same system as that used for the European system, PRR, due to its simplicity and ease of understanding; however, it has some limitations and issues which need to be considered during its interpretation:

• The VMD's system calculates the PRR based on the number of reports and not the number of individual animals (some reports may involve multiple animals).

• It is important to consider which data have been used as the background (denominator) data. Signals may occur due to changes in the background data even if no new cases for a particular product involving that VEDDRA term have been received.

• PRR tends to be sensitive especially when dealing with a low number of reports, leading to many false-positives.

The following criteria are used by TIGRESS in performing the PRR analysis:

- Results will only be valid if sufficient data are available, therefore the number of individual cases should at least be 3.
- PRR values greater than 1 indicate a higher probability for the considered VEDDRA term event to occur in animals treated with

the considered product compared to this event occurring with other products. However, due to the uncertainty surrounding PRR, only values of at least 2 are considered as potential signals.

- A lower 95% confidence limit above 1 indicates that the PRR is statistically significant.

Historically, the VMD has provided line listings of all serious reports to the UK Government's advisory committee for veterinary medicines, the Veterinary Products Committee (VPC), for their consideration. However, as a result of this new tool, from the beginning of 2013 only important signals will be discussed by the VPC which will significantly reduce the administrative burden of preparing such reports, and since this move coincides with a reduction of frequency of VPC meetings from 6 a year to 3 a year it is hoped that the longer period for analysis will lead to more meaningful results.

A future plan on the immediate horizon is to take on responsibility for monitoring adverse events to pet microchips, currently undertaken by the British Small Animal Veterinary Association (BSAVA). As it has recently been announced that microchipping of dogs will soon become a legal requirement in the UK it is anticipated that the need for more rigorous surveillance of implantation problems and chip failures will be required.

Ultimately and in the much more distant future, the VMD is considering the possibility of building on the concept of electronic reporting so that vets could send reports using pre-populated animal information, including treatment history taken from their practice management software but this would take a significant amount of resource. In the meantime the UK will continue to actively contribute to the development of Eudravigilance, which could provide greater benefits in the long term.

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