UK Trial Clearance Procedure Realigned with the Rest of the European Union

The requirements for a UK Animal Test Certificate (ATC or "field trial permit") were dramatically revised in December 2015, reinstating the UK as an attractive location for veterinary field trials. The changes introduced to the ATC system were significant in terms of approach to assessment, whilst still ensuring high levels of animal welfare. The new UK ATC application process has been greatly simplified, appears similar to that for many other EU member states, and is now aligned with the VICH Guideline 9 (Good Clinical Practice or GCPv).

The UK has long been a recognised location for the conduct of veterinary clinical field trials. Not only is the UK one of the largest animal health markets in Europe, the Veterinary Medicines Directorate (VMD) is also a very active and influential regulatory agency in the EU. The UK also boasts large numbers of highly-trained veterinary surgeons, including many specialists; has the largest national population of dogs in the EU, and of course it follows the international language of the animal health industry by speaking English. Indeed in the 1980s and 1990s, large numbers of field trials were performed by animal health companies in the UK, but this situation changed in subsequent years. More recently, many animal health companies have found it difficult to obtain UK trial clearance to perform their veterinary clinical trials, and others have suffered significant delays trying to meet the complex requirements of the old ATC system. It appears that this situation had sadly led to some animal health companies taking an active policy decision not to perform trials in the UK. With the recent positive revisions to the UK ATC system, it appears that finally, the long-held frustrations of many animal health company executives towards the UK ATC system should become a thing of the past.

So why have these changes happened? As a significant field trial provider in both the EU and USA, Triveritas has been heavily involved in the consultation process to make these regulatory changes a reality. Our substantial experience with the UK ATC system for over 15 years meant that Triveritas provided key objective information to the consultation process. For example, an impetus for requesting change was that identical trials for the same product were often starting animal recruitment later in the UK than in other major markets. A key factor affecting this situation was the complex and time-consuming obligations imposed by the old ATC system – which were not applied in other countries.

Fortunately, two major initiatives to improve the situation started almost simultaneously in 2012 and 2013. The VMD appeared to have started to reconsider its ATC guidance and the UK government announced an initiative to decrease any unnecessary bureaucracy (the "Red Tape Challenge"). Under this initiative Triveritas proposed that the UK ATC system should be reviewed. This proposal was adopted by the UK Cabinet Office and the potential benefits of the changes were highlighted on their website. A detailed consultation period followed and this included meetings with representatives from interested parties such as the Royal College of Veterinary Surgeons (RCVS) and the UK Home Office. All parties involved seem to share the same objective: the UK ATC process should be fit for purpose for use in the modern regulatory environment, whilst protecting animal welfare.

The VMD is recognised by the animal health industry as being willing to listen and consider all arguments before making decisions. This is likely to explain its predominance as a leading EU member state in some regulatory processes such as the EU Mutual Recognition Procedure (MRP) - where VMD has been consistently selected by animal health companies as being one of the most popular EU Reference EU Member States. It appears that the VMD carefully listened to all of the various concerns of the interested parties, considered the options, and released a new approach to the issue of ATCs which should become popular with animal health companies worldwide.

The new ATC guidance was published on 24th December 2015, and a standalone document outlining the revised application process was issued in March 2016. The new UK ATC system is now up and running, and given time, should result in an increased number of veterinary trials being performed in the UK.

The VMD has sensibly introduced at least four major changes which should transform the landscape for veterinary clinical trial clearances (ATCs) in the UK. A casual reading of the new guidance might not immediately show the notable departures from the previous system, but the changes are highly significant to both animal welfare and the animal health industry.

In the previous guidance, the VMD assessors had to consider if any procedure requested in the application might not be classified as "recognised veterinary practice"; where "RVP" is considered to be a procedure performed by a qualified veterinary surgeon in the UK during their routine work. Therefore any additional procedure required for a clinical trial (such as an additional blood sample to show the beneficial serological effects of a vaccine) was frequently considered as potentially outside of RVP. The VMD itself did not determine if the procedure was or was not RVP, and effectively the matter was referred to the professional body for UK veterinary surgeons (the Royal College of Veterinary Surgeons or RCVS). This immediately introduced a separate, independent professional organisation into the decision-making process for a UK ATC. The RCVS considerations were made by veterinary surgeons who very kindly provided their services on a voluntary basis, and this understandably but very

importantly meant that these considerations were not linked to any timetable or regulatory clock. Even more seriously, the RCVS considerations were made in isolation, considering only the issue of RVP but with no requirement to consider the results of a trial with respect to its usefulness to satisfy the safety and efficacy data requirements under EU Veterinary Medicinal Product Directive (2001/82/EC as amended) or those of the GCPv guideline (VICH Guideline GL9). If the RCVS determined that a procedure was not "recognised veterinary practice", then the VMD would not allow the procedure to be performed under an ATC. In order to circumvent this obstacle, the applicant could then apply to the UK Home Office to seek permission for the procedure (*e.g.* blood sampling), as this is the body which is responsible in the UK for the legislation for experimental animals found in EU Directive 2010/63/EC. This involvement of three organisations (VMD, RCVS, and Home Office) was considered unprecedented compared to other countries; and if the applicant persisted, a substantial amount of work, time and additional expenditure was required to meet the UK Home Office demands. Consequently, in such cases, the applicant frequently found the previous UK ATC application system was extremely unattractive compared to those available in other countries.

The second major change found in the new UK ATC system is a strong linkage to the requirements of VICH (or to give the full title, the "International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products"). The assessment of an ATC application under the new system will include a field trial protocol being reviewed by the VMD for compliance with GCPv in accordance with VICH guidance GL9, which considers safety and welfare as part of good (veterinary) clinical practice (GCPv). This alignment now means that the ATC review process will also consider safety of the animals, users, consumers, and environment; and also ensure animal welfare. This is logical, sensible and completely in line with modern industry practice. Furthermore, under the new system, before an ATC can be granted a benefit: risk assessment would be conducted based on submitted data, which again is in line with standard EU regulatory requirements and similar to the approach taken by many other EU regulators.

The third substantive change in the new ATC assessment system is a clear recognition that a minor routine procedure may be required in a clinical trial in order to generate suitable data regarding safety and efficacy of a product. In the new ATC guidance, there is a specific example mentioned of taking a blood sample prior to the administration of a veterinary medicine to establish a baseline for parameters. Also, the new ATC guidance indicates that subsequent sampling at key points following the administration of the veterinary medicine to monitor these parameters may be justified. This means that the expert assessors in the VMD

who are authorised to issue an ATC are now correctly given the responsibility of using their professional judgement to decide what is appropriate to be performed under an ATC. This principle is used in most countries and makes perfect sense because the assessors also understand the data requirements of their veterinary medicines regulations, as well as having a clear understanding of the safety and welfare requirements of VICH GL9 (GCPv).

It is hoped that this particular change by the VMD may enhance animal welfare by reducing the number of animals that are required globally for veterinary clinical trials, because it now means that many more protocols allowed in other countries (for example those concurred by CVM in the USA) should now also be acceptable in the UK. This should, in theory, increase the frequency of trials which recruit animals from sites in the USA and UK under a single protocol. Triveritas' experience of undertaking this type of study under a single protocol is that they can save both cost and time, as well as reduce the total number of animals used in a global clinical trials programme.

The fourth and final major change is less obviously found, being written in the separate document on how to apply for an ATC. There is a new, sensible, and understandable focus on the owner informed consent form. This is to document the owner's willingness to allow their animal to participate in a particular study, after having been informed of all aspects of the study which are relevant to that decision. An example of the owner consent form must be submitted as part of an ATC application under the new system. Again, this is in total harmony with the international approach of the VICH GCPv GL9. Whilst this new requirement has major implications regarding the assurance of animal welfare, it has minimal impact on the amount of work required by the applicant. Currently the owner informed consent form should use understandable language so the owner is not confused by veterinary or medical jargon, and must include at least the following: the owner's consent; an explanation of the nature of the trial and the purpose of treatment; notification that the trial uses a medicine which has not been authorised and if a negative control or placebo is included their animal may not receive treatment as part of trial; and importantly, that they may withdraw their animal any time without any prejudice to the future veterinary care of the animal. The new ATC guidance adds two further items to the informed consent form: a statement from the veterinarian concerned confirming that if the animal is not responding to treatment that they may treat the animal at any time to maintain the appropriate level of veterinary care; and confirmation that the owner has fully understood the consent form. By following the approach of the VICH GCPv guideline and making specific but reasonable requests to the applicant, the VMD has cleverly ensured that the owner has full awareness of the situation; additionally, the expert professional judgement of the concerned local veterinarian is correctly pivotal to the welfare of the trial animals. All in all, a very sensible approach.

The new UK ATC system maintains its flexibility regarding the types of ATC that can be granted in the UK, as before. There is the Type S ATC which is designed for small-scale non-commercial trials involving no more than 50 animals using registered human or veterinary pharmaceutical products. The new guidance indicates that trials conducted under a type S ATC should, where possible, be conducted in accordance with GCPv.

The Type A or Type B ATCs are appropriate for companies wishing to generate data to support an application for a marketing authorisation for a veterinary medicine. For trials to be conducted under a Type A or a Type B ATC it is required to confirm that the trial will be carried out in accordance with GCPv. The Type A ATC procedure is used where the product is already authorised as a human or veterinary medicine in the EU or EEA, plus further reasonable requirements which are unchanged from the previous guidance. The Type B ATC procedure is used if the criteria for the Type A procedure are not applicable – *i.e.* everything else.

In conclusion, the UK VMD has issued new guidance for a new system on how to obtain a UK ATC. There are major changes from the previous system which mean that the UK is likely to become an increasingly important country for veterinary clinical trials. Consequently, animal health companies should review their attitudes to the UK ATC system which is now aligned with the approach to issuing trial clearances in other countries. The changes include a streamlined single agency approach; alignment with the requirements of VICH GL9 (GCPv); further measures to ensure animal welfare is protected including an increased emphasis on the owner informed consent; and a clear recognition of the need for scientifically justified baseline and subsequent samplings. The new guidance correctly gives the VMD assessors both the responsibility and authority to issue ATC under a much improved scheme.

Julian Braidwood is Managing Director of Triveritas which is a contract product development company offering a comprehensive range of services to the Animal Health industry. Since qualifying as Veterinary Surgeon in 1982 Julian has worked in all aspects of product development with five different veterinary pharmaceutical companies. He has been involved in the registration of a large number of veterinary products internationally and has worked with all of the key Regulatory Authorities.
Email: julian.braidwood@triveritas.com