Animal Pharm
Agribusiness intelligence

The evolving regulation of veterinary medicines in Europe: Progress or bureaucracy?

by Dr Anja Holm

Last year saw a significant step towards modernized legislation governing veterinary medicines in Europe. But how does this new regulatory horizon fit into the history of guidelines for animal health? Anja Holm – founder of Central VetPharma Consultancy and chief executive of Panion Animal Health, collaborative partner for Cyton Biosciences and former head of the European Medicines Agency's Committee for Medicinal Products for Veterinary Use – provides a holistic view of the regulations that govern animal health.

Around 60 years ago, a scandal arose in the medicines industry that reverberated around the world. Over 10,000 children were born with deformed limbs and other birth defects, due to the drug thalidomide being given to pregnant women in the early weeks of pregnancy.

The tragic outcome led to the development of much tougher regulation of medicines in Europe by Directive 65/65/EEC, which required that proprietary medicinal products for use in humans or animals could only be marketed after an authorization procedure based on specific tests and trials.

Now in 2018, we are seeing the latest veterinary medicines legislation being adopted with a vastly higher level of detail and comprehensiveness. What happened in the intervening period and why is it important for companies to understand the development of veterinary medicinal product regulations?

Legislative review process

At approximately 10-20-year intervals, updated rules for authorization of veterinary medicines have emerged for implementation. Until now, the format has chiefly been EU directives, which are transposed into national law in each member state.

In an effort to avoid the variability this process can inherently cause, the forthcoming new legislation was proposed as an EU regulation – for which the text will be immediately valid in all member states.

In 2001 (and again in 2009), the technical requirements were comprehensively rewritten and further details given, specifying to companies very precise legal requirements that must be fulfilled when they plan their marketing authorization applications.

In addition, many guidance documents have been drafted and published over the years by the regulatory authorities with the intention to help industry perform adequate and acceptable studies and to avoid rejection of study results (due to deficiency in study design, for example).

The legislative review process involves a consultation stage, where industry and other stakeholders are invited to comment. This provides a grounding in the 'real world' of the animal health industry, so requirements that could be overly burdensome – or even unachievable in practice – are (hopefully) removed from the draft texts.

The adopted guidance documents may seem onerous at first view but they do promote consistency in requirements, and may hold the assessors' focus on what aspects of the dossier data are 'need to know' – avoiding requests for scientific information that is just 'nice to know'.

Coexistence of old products and new products

It is clear from a review of authorized Summary of Product Characteristics texts that older products were permitted to have much broader claims and less specific warning texts than newer products authorized under more stringent requirements and with tougher scrutiny by assessors. For example, old antibiotic products may have claims as broad as "For treatment of infections caused by bacteria sensitive to oxytetracycline".

Newer antibiotics will have narrower claims listing the precise condition, plus the specific bacterial species involved – necessitating detailed studies. This incongruence represents an advantage to the marketing authorization holders that own these older products, which can still retain broad claims that would probably not be approved in a regulatory assessment now.

The co-existence on the market of such differences within the same group of medicines reflects the advancement of science over the years, the development of regulatory scrutiny and demands, but also the inertia of the established system, where a re-assessment and updating of all old products would be an insurmountable challenge for both industry and regulators.

Moreover, such re-assessment would likely lead to the loss of many medicinal products that currently function well on the market, due to the high costs of having the scientific data produced and the paperwork updated.

Food safety and medicine residues

When food-producing animals are treated with veterinary medicines, it is necessary to wait for the residues to be 'washed out', so the animal-derived food (e.g. meat or milk) is once again safe for the consumer – the so-called withdrawal period.

In the 1990s, the legislation on residues from veterinary medicinal products was rewritten, and a new requirement was brought into force for scientific evaluation of the maximum residue limit (MRL) of any veterinary medicinal substance permitted in foodstuffs. This was done in the interest of consumer safety and to eliminate barriers to free trade of food.

All authorized and new substances for use in food animals were re-evaluated for the safety and residue profile of the substance. If the substance was not defended or the data were inadequate to reach a conclusion, products were taken off the market.

Over 700 MRL dossiers were submitted by marketing authorization holders and evaluated by groups in the European Medicines Agency (EMA) over the course of just a few years – a huge work effort. Nevertheless, many substances were left without a valid MRL, and numerous companies lost profitable products from their portfolios because they were unable to comply with the requirement.

A direct consequence of this and a major issue in terms of animal welfare, was reduced availability of medicines to treat diseased animals – particularly for smaller market sectors such as turkey production, fish farming, equine husbandry and products where the investment to defend the substance was estimated to be higher than the expected return on the product.

There were several reactions to this availability crisis by regulators, one being extrapolation rules for MRLs, which have been developed over the years and are now established in legal text. Additionally, a scheme was established for Minor Use, Minor Species (MUMS) products, which is administrated by the EMA and comprises financial incentives and reduced data requirements, as well as increased assistance from the regulator. This initiative has been successful over the years since its introduction and has resulted in several new products being authorized.

EU expansion and establishment of the EMA

At the same time as the medicines legislation was expanding, so was the European Union and its internal structure. The EMA was established in 1995 and serves as the secretariat for the pan-European expert groups and committees involved in medicines evaluation.

Here, the option of central authorization of medicines (i.e. one authorization by the European Commission, which is valid in all member states) was developed with an efficient system of one assessing rapporteur and one co-rapporteur, each with their assessing team, who would evaluate an application on behalf of all the other member states represented.

This allowed cooperation and efficiencies through division of workload, and encouraged trust between scientists and assessors due to the systems of commenting on assessments and voting on decisions. The scientific working groups, covering a diverse range of topics, expanded the network of experts and pooled expertise from all over the EU for the benefit of all member states – particularly the smaller member states with fewer domestic resources at home.

Cooperation between regulators

In the earliest stages of medicines authorization, all medicines were approved nationally by the national competent authority (NCA) of a member state. Later came the option to 'mutually recognize' product authorizations from another member state and lastly, the decentralized procedure for new product applications became available to companies, with several member states involved in a simultaneous assessment.

The old national assessment procedures, without communication between NCAs, have often resulted in variability across territories (e.g. dose, warnings or withdrawal periods) for identical products in different national markets. This is difficult to explain to European vets and users.

Most medicines are still nationally authorized, due to established products remaining on the market but slowly the proportion of products harmonized through mutual recognition or decentralized procedures is increasing.

Finding agreement on a harmonized claim and labelling for a product requires good cooperation between the member state institutions. Around 20 years ago, the Heads of Medicines Agencies (HMA) was established to increase this cooperation and harmonization and today it consists of 46 NCAs.

It serves as the forum for coordinated efforts in strategy and high-level discussions, and as the official body of the Coordination Group for Mutual Recognition and Decentralised Procedures, Veterinary (CMDv). The CMDv handles scientific evaluations and mediates disagreements between the member states involved in mutual recognition or decentralized authorization procedures.

In the 'Strategy to 2020', the EMA and HMA for the first time coordinated their work to a common statement of short- and long-term goals and intentions. This is an important milestone in drawing together the European network of regulatory agencies and will increase the effectiveness in areas of common priority, such as fighting the increase of antimicrobial resistance and improving pharmacovigilance for veterinary medicines.

Global harmonization

A company that develops a veterinary medicine for the European market naturally wants to have clear rules, so a robust development plan can be drafted and followed – ensuring no unpleasant surprises emerge (e.g. unforeseen data requirements) that could set the process back.

From the beginning of the regulation of medicines up to the present day, the legal requirements have clearly increased. However, they have also become more harmonized globally. This means if a study is carried out for one country or region and it follows a harmonized guideline, it will also be accepted in other regions of the world.

The efforts that have enabled this come from the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products). The VICH cooperates with the OIE and consists of industry and regulators from founding members the EU, US and Japan, as well as Canada, Australia, New Zealand and South Africa as observer members. An outreach initiative intends to include other regions across the world, with the ultimate aim of more than 50 globally harmonized guidelines being accepted worldwide.

Regulation keeping pace with scientific advancement

There is a public expectancy and pressure for safe and efficacious medicines to treat animal diseases, and the responsibility for such medicines to be available must be borne by both industry and the regulators.

A lot of attention has been given to the reduction of risk from antimicrobial resistance in the veterinary field, both from zoonotic bacteria that may be transferred to humans from animals and for maintaining the possibility to cure bacterial diseases in animals.

This fight will continue to be a priority based on the new veterinary medicines legislation that is expected to come into force in the EU approximately three years from now. A lot of other topics are also waiting for a solution, such as rules for innovative medicines that currently fall outside of the standard legal frameworks. These clearly need to be regulated in a balanced way, so we neither halt innovation nor risk animal or human health.

Conclusions

Over the last few decades, the legal framework and the EU network for medicines has developed into an increasingly complex web, the mechanics of which keep the bar high for products to enter the European market.

It can be difficult for companies to meet the required standards, follow all the detailed guidance, and engage properly with the assessment procedures along the route from product development to the EU market but the line between 'cutting red tape' and 'burning the books' can be quite a fine one.

Businesses need room to maneuver and costs to them should not stifle growth or innovation. However, maintaining safety is essential.

There is a lot to be said too for the existence of such rules in providing clarity and a level of certainty for companies when making key decisions such as where to allocate budgets or how to plan appropriate supporting studies.

With the new veterinary regulation just published, we are entering a new phase of consultation regarding the numerous implementing and delegated acts, which will add critical details to the final requirements for developing and registering veterinary medicines. It should be noted a degree of caution is advisable during this consultation, to avoid re-writing existing rules simply for the sake of it. There are good reasons why the rules came about in the first place, and over the years industry becomes familiar with them and accustomed to working in their context. The upheaval of implementing and factoring in major legislative changes is a burden too.

The sometimes-challenging regulatory environment for veterinary medicines in the EU has improved the safety and quality of veterinary medicines on the market. It has also pooled the best expertise and work-power from all of the EU member states, avoided duplication of effort and harmonized a lot of the regulatory and scientific requirements, which in the end is of benefit to the industry.