PEER REVIEWED

The Long and Winding Road to Better Legislation for Animal Medicines

In the European Union, an effective and rigorous examination and registration system exists for placing any veterinary medicine or animal health product on the market. An independent scientific review of a comprehensive data package has to be carried out by the authorities to ensure products are safe, of high quality and efficacious. Only after this review has been carried out may a product be granted a 'marketing authorisation'. This registration process ensures that only products that satisfy the defined standards reach the hands of Europe's veterinarians, farmers and pet owners to care for their animals.

Dating back to 1965, the European Community Medicines Directive[1] laid down three basic criteria on which decisions regarding marketing authorisation are based. These are: safety, quality and efficacy. Over the past 50 years, requirements in terms of these three criteria have been updated continually in line with advances in scientific knowledge and risk management.

Now, Europe is at the crossroads for further updates to the rules governing the authorisation of animal medicines and medicated feed. Nearly eight years ago, back in 2010, the European Commission carried out a public consultation to review the current procedures and look at how to put in place a simpler legal framework, safeguarding public and animal health while both increasing the availability of veterinary medicines and reducing the administrative burden of the registration process. This was followed by a study to quantify the main perceived problems with the current system, to suggest policy options to resolve these problems, and to assess the impact of a revision of the veterinary pharmaceutical legislation.

Does the Current EU Framework for Veterinary Medicines Approvals Need to be Revised?

The resounding response from any company who has had to navigate the complex EU marketing authorisation procedures will most certainly be yes! The impact assessment commissioned by the European Commission and published in 2011 identified problems in four broad areas: the availability of medicines; the need to stimulate innovation; the operation of the single market; and the administrative burdens imposed on companies and regulators.

The current process requires applicants to submit data supporting the safety, quality and efficacy of a product in a detailed dossier, which is reviewed by an independent scientific committee working on behalf of the governmental agency. Each EU member state has its own regulatory authority, authorised to perform independent scientific evaluations of veterinary medicinal products. The member states are required to work collaboratively together in a 'decentralised' or 'mutual recognition' procedure. In addition, the European Medicines Agency (EMA) serves as a pan-EU regulatory agency offering a 'centralised procedure' for certain innovative animal and human medicines, and has been praised as global best practice.

However, although registration requirements and procedures have been harmonised within the EU, the biggest challenge facing the decentralised procedures is the disharmonised interpretation and implementation of requirements by the member states, and a certain lack of trust, causing the procedures to become less efficient. In addition, the costly data requirements and lengthy registration procedures present challenges to the development of medicines for small or limited markets (such as the market for minor species or rare diseases) and for emergency situations (such as a vaccine to control a new emerging disease).

The procedures are being continually improved through the collaborative efforts of stakeholders and national competent authorities to identify and address problems as they arise. Nevertheless, the 2010 public consultation identified the need for a significantly improved legislative framework.

The subsequent impact assessment estimated, using the European Commission's standard cost model, that the administrative burden placed on the veterinary medicines industry by the product registration system represented 13% of the sector's turnover. This was a major reality check for the European Commission, as this figure far exceeds other sectors and is more than double that experienced by the human medicines sector at 6% (despite its highly regulated nature). Consequently, the reduction in administrative burden became a central theme to the subsequent legislative proposals from the European Commission.

Opportunities for Improvement Post-authorisation

Once a veterinary medicine is authorised, the biggest hurdle preventing it being made available for use in smaller member states is the cost of country-specific packaging in the local language, which can make the cost of placing a product on the market uneconomical. Current legislation is very prescriptive about the information that must appear on the various packaging elements (such as immediate label, carton packaging, and pack leaflet) and is a hindrance to the development of multi-lingual labelling. In fact, packaging was identified as the largest item contributing to the high administrative burden, and became another focus of the review of the legislation.

Once a product has been authorised and placed on the market, certain regulatory obligations exist during the life-cycle of the product. These include submitting variations to and renewals of marketing authorisations, and maintaining a pharmacovigilance system. The EU systems and the EU structure with 28 member states result in the highest cost anywhere in the world for 'defensive R&D' and maintaining products on the market. In addition, the simplification of the pharmacovigilance system was also identified as a good candidate for the reduction of administrative burden, given the current system's resource-intensive requirement for regular reporting even in the absence of adverse events.

Impact on Innovation

Speaking of R&D, in the past 10 years the increase in R&D costs to develop animal medicines has risen significantly. The R&D cycle can take as long as 10 years and costs can elevate up to €150 million. The time needed to develop a new product for livestock in Europe, for example, increased by six years over a 15-year period (1990–2005), with costs more than doubling in this time[2]. This increase in investment costs necessitates a corresponding increase in periods of protection of the technical data from generic competition.

However, the biggest factors adversely impacting innovation in new products are: (a) the amount of the R&D budget that must be diverted to defending and maintaining existing products, and especially the costs of manufacturing, compliance and variations; and (b) the increased generic competition created by the introduction of the 'global marketing authorisation concept'[3]. Since the introduction of the 2004 Directive[4], investment in new product development has significantly decreased by 20% (from an industry average of nearly 10% of turnover, to 7.8% of turnover).

A combination of: (a) reducing the information that must appear on the immediate label (e.g. with the use of certain standard abbreviations and the judicious use of pictograms) to facilitate multi-lingual labelling and lower the hurdle of packaging and labelling costs for individual countries; (b) a science-based risk-benefit system to avoid repeating studies; (c) adapted protection periods for technical documentation when developing new products and line extensions; and (d) a new pragmatic system to overcome the lack of harmonisation in the authorised summary of product characteristics – could help to improve the availability of veterinary medicines.

A Long-overdue Revision is Proposed

It has been very clear to all those involved in the current review of the veterinary medicines legislation that good legislation facilitates innovation, which in turn results in new or better diagnostics, vaccines and pharmaceuticals being made available for use by veterinarians, farmers, pet and other animal owners, throughout Europe. So, following the Commission's impact assessment which confirmed the problematic issues identified since implementation of the 2004 Directive, animal health companies across Europe patiently waited to see what the new proposal would entail.

After three more years of deliberation, the European Commission finally published a package of proposals in September 2014 for two new Regulations covering veterinary medicinal products and medicated feed.

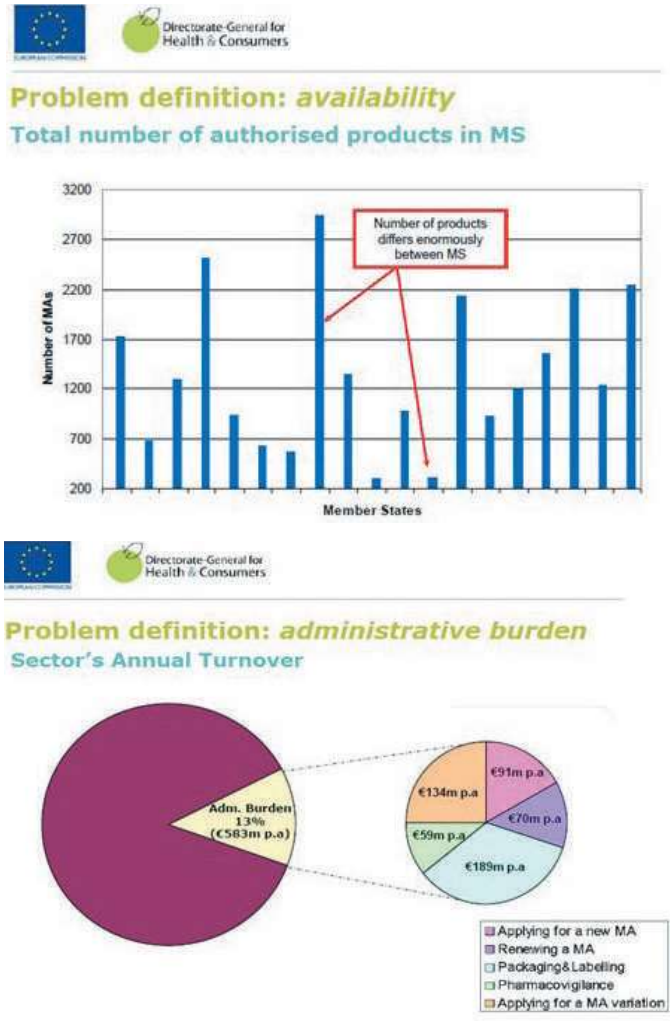
The proposal on veterinary medicinal products was published with the headlining objectives to:

- Increase the availability of veterinary medicinal products;
- Reduce administrative burden;
- Stimulate competitiveness and innovation;
- Improve the functioning of the internal market; and
- Address the public health risk of antimicrobial resistance.

The proposal on the modernisation of medicated feed legislation now also includes medicated feed for pets in its scope, a useful treatment route for any well-scratched cat owner! The medicated feed proposal mainly aims to ensure a harmonised approach to product quality and safety in the EU, while simultaneously paving the way for better treatments for animal illnesses.

The third part of the package of legislative proposals will amend Regulation (EC) 726/2004[5] to take into account the fact that centralised marketing authorisation for veterinary products is being separated from that of human medicine. So the overall thought-process behind the revision was about ensuring a more tailored process that would better reflect and be adapted to the specificities of the animal health sector. This more tailored approach would then stimulate innovation for the benefit of animals – including aquatic species, animal keepers, pet owners, veterinarians and businesses – including farmers and the animal health industry.

Following the publication of this package of proposals, the European Parliament and Council started their reviews of the proposed new Regulations. The Parliament agreed on a number of amendments in March 2016 which seemed in line with the general goal of ensuring the availability of a varied arsenal of veterinary medicines for the prevention and treatment of animal disease. The European Council deliberations continued well into 2017, but the Estonian Presidency took up the dossier with vigour in the second half of the year and the mandate was agreed for trilogue negotiations with the Commission, Parliament and Council on the final text to begin onwards of January 2018.



Can the Proposed New EU Rules Improve Availability of Animal Medicines in Europe?

It is clear that a revised system, more tailored to the characteristics and needs of the veterinary medicines sector, could go a long way to help improve the availability

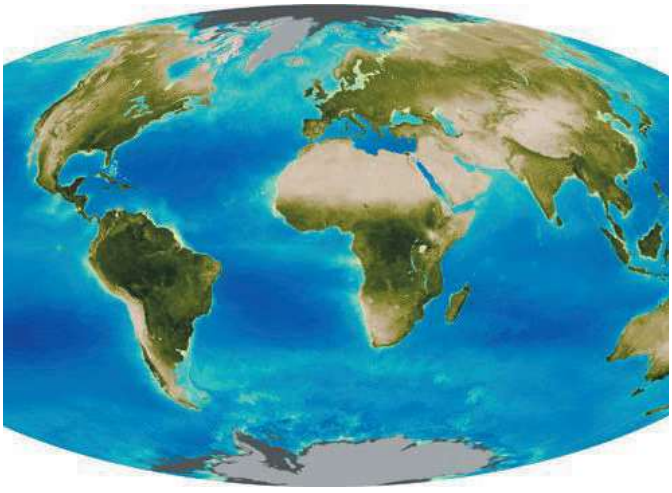
of animal medicines in Europe. Like with any innovative business, the animal medicines industry can only effectively operate in an environment which gives companies the confidence to invest in the research and development of new products and technologies. The proposed legislation makes firm steps towards streamlining procedures, which should help to reduce some of the administrative burden and speed up the entire process of bringing innovations to market.

Efforts made to address issues related to harmonising key documentation and reducing administrative burden to increase medicines availability are well-intentioned and appreciated. Several aspects of the legislation are still being fine-tuned, of course, and AnimalhealthEurope has identified some watch areas that could still have an impact on stimulating innovation.

Rules for marketing authorisations in the future must remain based on a risk/benefit analysis of a finished product and not a hazard-based approach of an active ingredient. Reviews based on the potential hazard of a substance within a product, rather than a risk/benefit review of a finished product, may be grounds for immediate refusal of a licence, meaning no treatment available and a waste of resources.

Further research and the use of biotechnology can also lead to improved stability of products or deliver more effective and simpler routes of administration. New developments in formulation technology, for example, can bring significant improvements in animal health solutions, but applying these improvements to existing products requires a major investment, as regulatory studies need to be repeated, and there is currently no data protection period for such advances. The proposal offers a four-year protection period before a second company can cross-refer to the originator's new data – limited to antibiotic products only. The animal health industry recommends that this proposal be opened up to all products as the role of other important product classes, such as parasiticides, needs to be recognised.

Antibiotics are also a central focus of the proposed legislative package, with many EU actors eagerly expecting rules that will help address global concerns of the development of antibiotic resistance. It remains important to point out that proportionate and science-based regulation is required if we are to adequately supply our farmers, pet owners and veterinarians with the tools they need to keep our animals healthy, to safeguard their welfare, and to sustain our agri-food economy. Any restrictions placed on the use of veterinary antibiotics should therefore be determined on the basis of European scientific recommendations, i.e. those provided by the European Medicines Agency (and not the World Health Organisation) and that seemingly interchangeable definitions of veterinary antimicrobials and antibiotics do not lead to confusion.



Ensuring the competitiveness of Europe's industry by reducing the high administrative burden, streamlining procedures and supporting innovation, can go a long way to making this long-travelled road to better regulation worth it.

More New and Improved Medicines for Better Animal Health in Europe

Fostering innovation through a harmonised system, where resources can confidently be invested in R&D, means that new medicines can be developed to fill gaps in treatment options. By rewarding investment in innovation through improved protection periods for technical documentation, harmonising processes for registering and authorising medicines, and with the right people making science-based decisions in the interests of animal health and welfare, the animal medicines industry can respond to Europe's need for new and improved tools to better manage animal health and prevent disease.

Simply put, by putting in place legislation that is conducive to innovation, we can invest more in research and development. This would lead to a wider availability of more medicines, for more species, in more countries in Europe, making the veterinarian's job just that little bit easier.

REFERENCES

1. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products
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3. See article 5.1 of Directive 2001/82/EC, as amended by Directive 2004/28/EC
4. Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products
5. Regulation (Ec) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

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With membership covering 90% of the European market, AnimalhealthEurope represents innovators and generics alike, as well as large, medium-sized and small companies.

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