PEER REVIEWED

Global Initiatives Promoting Good Regulatory Practices for Veterinary Medicines

In this edition the World Bank Group (WBG) reports on its long-term project 'Enabling the Business of Agriculture' (EBA)[1]. The driving force behind this project is the importance of agriculture to the WBG's twin goals of ending poverty by 2030 and boosting shared prosperity. Since 2013, the project has collected data from 62 countries on laws and regulations that impact the business environment for agriculture across 12 topic areas. The 3rd project report was published by WBG in February 2017[2], and for the first time includes a chapter on 'Livestock' covering the regulatory environment for the market control of veterinary medicinal products (VMPs).

The objectives of the 'Livestock' project correspond with the Vision[3] of HealthforAnimals, the global animal medicines industry association, for globally harmonised regulatory systems and its objectives to promote regulatory convergence. So the opportunity is taken to briefly review what other projects and organisations are actively seeking to promote good regulatory practices for the benefit of animal health and all those who depend on their pets and livestock.

The Importance of Agriculture to Human Health

The importance of agriculture cannot be over-stated. The demand for food is increasing 20% annually to feed a growing world population that may reach 9 billion by 2050[2]. The largest increases in demand are projected in Sub-Saharan Africa, South Asia and East Asia. Boosting the productivity, profitability and sustainability of agriculture is essential to support this growth.

But agriculture is not just important for a secure food supply. For some 500 million smallholder farmers, it is their economic and social life-blood; and for subsistence farmers in developing countries it is essential to their survival and the largest source of incomes, jobs and food security. That is why the World Bank Group's 'Enabling the Business of Agriculture' (EBA) project is such an important tool to improve prosperity and end extreme poverty.

The world needs more productive, sustainable and efficient ways to grow food. We need systems to support the resilience of farmers and food supply chains while simultaneously reducing the environmental footprint of agriculture. These systems cannot function properly without a framework of good regulations and infrastructure, which can create well-functioning markets, fostering growth in agribusinesses.

In short, the world needs a food system that can feed every person, every day, everywhere with a nutritious and affordable diet, delivered in a climate-smart, sustainable way.

Livestock and the Regulation of Veterinary Medicines

If you are raising livestock, you need access to certain 'inputs', including feed, water and disease control. Disease is estimated to cause 20% of livestock production losses globally[4]. This can have knock-on effects and put public health at risk by impacting food security and because 70% of all new human diseases are zoonotic, often originating from animals[5].

Maintaining livestock health by improving access to veterinary medicinal products (VMPs) can minimise the negative economic impact of diseases and safeguard the livelihoods of millions of farmers around the world. For this we need an enabling regulatory environment that encourages and does not hinder product registrations; we need effective market control to enforce quality standards and prevent fraud; we need the necessary infrastructure for supply and distribution; and we need good veterinary services for disease identification and to ensure effective and safe use of the VMPs. Open borders, inadequate legal frameworks and poor law enforcement can lead to counterfeit and substandard VMPs in the market. Counterfeit VMPs are a major threat to animal health and disease control.

For the regulatory framework to support a reliable market in effective and safe VMPs of guaranteed quality, it needs to cover the full supply chain of manufacture, registration, import, distribution, sale and/or administration of livestock medicinal products.

Enabling the Business of Agriculture Project

This is why the WBG, with its twin goals of ending poverty by 2030 and boosting shared prosperity – as well as the Sustainable Development Goals – has invested significant effort in the EBA project. The main aim is to measure and monitor regulations that affect the functioning of agribusinesses, covering all aspects across 12 topics, from seeds to machinery to finance.

The extensive and thorough nature of this World Bank survey, which aims to expand to cover 80 countries in 2018, makes it an important and influential tool in the drive to reach this goal through global convergence towards regulatory best practice. Their governments should make good use of this valuable benchmarking.

The EBA 2017 report[2] catalogues the level of transparency, predictability and efficiency of the regulatory systems in a wide sample of countries. These factors influence private sector decisions to supply a market with VMPs, and thus directly affect their availability to veterinarians. It is important that countries have the systems and infrastructure in place to legally register VMPs, to control the marketplace, and protect consumer health.

Other Regulatory Convergence Projects

HealthforAnimals has been running similar, albeit smaller, projects aimed at promoting regulatory good practice and regulatory harmonisation, through its series of five-yearly Global Regulatory Benchmarking Surveys[6]. HealthforAnimals is also a driving force behind a series of Global Animal Health Conferences and workshops[7,8], sponsored by the Bill and Melinda Gates Foundation, and global harmonisation initiatives such as VICH[9].

The most important player, when it comes to promoting global animal health, is The World Organisation for Animal Health (OIE), which was established in 1924 in recognition of the need to fight animal diseases by coordinating at a global level. Of equal influential standing is the World Health Organisation, which is developing guidelines for national regulatory authorities on good regulatory practices[10].

Examples of Good Regulatory Practices

- Develop regulations that are flexible,
- Use risk management principles,
- Be consistent in guidance and decision-making,
- Be efficient in information and records management,
- Measure and maintain performance and transparency,
- Be approachable, open to dialogue and reach out to stakeholders,
- Be aware of changing regional and global factors in R&D and access to drugs.

All these activities are reviewed below. However the starting point for HealthforAnimals was the elaboration of its "Global Vision".

The HealthforAnimals Vision

The HealthforAnimals "Global Vision for the harmonised Regulation of Veterinary Medicines across the World2" 'identifies 10 key elements (see below), but can be concisely captured as:

"Efficient regulatory systems that result in harmonized, science-based decisions in predictable timeframes, resulting in the wide availability of safe and effective veterinary medicines."

The ten-point plan supporting the HealthforAnimals Vision

1. Authorisation decisions are science-based solely on evaluation of benefit and risks.
2. Predictable regulatory timeframes, with a maximum of 24 months for a new product.
3. Regulation that is efficient for industry and regulators, with no unnecessary administrative burden.
4. More countries/regions co-operating on the core assessment of the same product, or mutually recognising assessments from other countries/regions.
5. A fair return on investment for innovation. Maintaining confidentiality of data and awarding appropriate periods of protection of data.
6. Regulatory frameworks and regulatory staff which can manage highly innovative products/new technologies.
7. Ability for companies to undertake global developments, with a core set of data and studies meeting the needs of all countries/regions. VICH conducted studies being accepted by all countries.
8. Ability to locate manufacturing anywhere in the world, operating to a single set of standards. More mutual recognition agreements on inspections.
9. A single global system of pharmacovigilance with requirements and approach aligned with the relevant VICH guidelines and the Guide to the Essentials for Veterinary Pharmacovigilance[7].
10. Countries to have legal frameworks which includes management of urgent off-label use and a legal basis to deal with illegal (or illegally supplied) veterinary medicines.

To maximise innovation and the availability of medicines to animals and customers, it is important to remove unnecessary administrative burdens and to achieve regulatory convergence between countries/regions. The HealthforAnimals Global Benchmarking Survey Reports, which preceded the World Bank surveys, provide some good pointers for the challenges that need to be addressed and identify the future needs for well-functioning global regulatory systems.

Global Benchmarking Surveys

Every five years since 1996, HealthforAnimals has commissioned a global survey to review and benchmark, from the perspective of its member companies, the status of the different regional regulatory frameworks for veterinary medicines and the impacts these have on the industry's ability to invest in veterinary medicinal product development. The reports identify global best practices and reveal the most common regulatory barriers shared by animal health markets worldwide.

The most recent Global Benchmarking Survey (GBS) report, published in June 2016, covers six countries and one region (Australia, Brazil, Canada, China, Japan, USA and EU). The report reveals significant differences between countries or regions, for example in terms of maturity of the regulatory framework, the different types of application procedures available, the different ways in which changes to products are managed, the approach to monitoring safety and efficacy of products after registration, the transparency of the authorities and resources available to the authorities.

Many of the differences are fundamental and are based on different philosophies and a level of trust placed in the veterinary pharmaceutical industry. It is not simply that some authorities have lightweight versions of the framework used in other regions; the frameworks themselves differ.

The veterinary pharmaceutical industry continues to consolidate through mergers and acquisitions. Funding for research and development (R&D) is under intense pressure, particularly to support veterinary medicines serving small markets, whether in certain countries, for certain species or for particular diseases. The cost of development of a new veterinary medicine for use in food animals is very high. In addition, a proportion of the available R&D budget in companies must be used to maintain the licences of existing products (known as 'defensive R&D'); this is a particular problem in Europe (see graph), and regulations should aim to limit this to the level absolutely necessary.

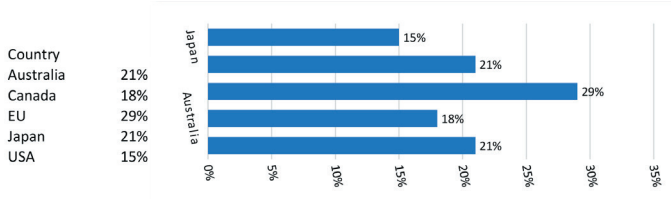

Figure 1: Proportion of R&D budgets spent on 'defensive R&D' in VICH regions

Global Animal Health Workshops

Other organisations interested in promoting animal health through good regulatory systems, such as OIE, GALVmed and the regulatory bodies that are part of VICH (USDA, FDA, EMA and JMAFF), have recognised the importance of good governance in the regulation and control of veterinary products and the part this plays in supporting socio-economic development, public health and animal health.

This serves the wider aim of promoting the One Health approach towards human and animal health.

With this common set of objectives in mind, HealthforAnimals has worked with these bodies to develop conferences and workshops for the African and the South Asia region. The aim was to share knowledge and understanding of good regulatory practices and to promote further close cooperation amongst a regional network of regulatory agencies (see box below).

Themes addressed in the Global Animal Health Workshops

- The essential elements of a regulatory system for the registration of veterinary products,
- The opportunities for stimulating the entry of new quality assured, safe and effective products on the market,
- The roles of legislation and guidance documents, and alignment with international standards,
- Good manufacturing practices (GMP), authorisation procedures for veterinary products and pharmacovigilance,
- The benefits and hurdles of mutual recognition of marketing authorisation processes from other regions with internationally recognised regulatory systems, including GMP,
- The benefits and hurdles of the formation of regional organisations to pool resources and the advantages of alignment with international standards,
- The processes necessary for market control of veterinary products and how to tackle falsified products.

The underlying themes were two-fold: firstly, the relationship between animal health and access to veterinary products, and the need to ensure the regulatory environment is enabling for manufacturers of veterinary products; and secondly, the value, in terms of efficient use of resources and encouraging market development, of working to international standards and guidelines and regulatory convergence, particularly on a regional basis.

Other Areas of Industry Standardisation

In addition to the regulatory framework, there are other interesting areas connected to bringing veterinary medicines to the market where HealthforAnimals is actively promoting a single harmonised approach. For example, it has developed:

- Regional templates for the contents of the data dossiers required for an application for marketing authorisation,
- A harmonised approach to pharmacovigilance based on the VICH guidelines,
- A unified approach to the use of a 2D matrix barcode for product labelling,
- A copyright-free set of species pictograms for use on product labelling.

HealthforAnimals is also actively promoting a harmonised approach to GMP inspections through the PIC/S organisation and a harmonised approach to the protection of proprietary data submitted to competent authorities in the marketing authorisation dossiers.

VICH

VICH is a trilateral (EU-Japan-USA) programme, formed under the auspices of OIE, with active participation also from four observer countries (Canada, Australia, New Zealand and South Africa), with the purpose of 'International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products' (to give VICH its full name).

The role of VICH is to develop harmonised guidelines on the technical details of the studies to be submitted in the data dossier for applications for marketing authorisation (also known as 'product registration'). The benefit of having harmonised guidelines is to avoid studies being duplicated or repeated for products being registered in more than one country. Typically, a VICH guideline describes how a study should be conducted to satisfy quality, safety or efficacy data requirements.

In the period from its establishment in 1996 to November 2017, VICH has published 56 harmonised guidelines (www.vichsec.org), with a further six guidelines in preparation. The guidelines cover the areas:

- For pharmaceuticals: quality, safety (toxicology, target animal safety, antimicrobial safety, environmental safety and residues) and efficacy.
- For biologicals: quality, target animal safety and batch safety testing.
- In addition, there is one general guideline on Good Clinical Practice (GCP), one guideline on the electronic format for electronic submission of dossiers, and five pharmacovigilance guidelines.

VICH Outreach Forum

One of the primary objectives of VICH is to provide a basis for the wider international harmonisation of technical requirements, improve information exchange and raise awareness of the VICH guidelines outside of the participating countries. This has always been achieved using the OIE's channels of communication to OIE member countries, but in 2006 more direct lines of communication were opened up with the creation of the VICH Outreach Forum. This allows country delegates to interact directly with VICH Steering Committee members in a workshop-style setting and to also network with each other.

The VICH Outreach Forum is composed of countries and regional organisations that have an operational regulatory system, have expressed an interest in the work of VICH, and are motivated to participate in the activities of the VICH Outreach Forum. Currently 20 countries and four regional organisations are participating.

The VICH Outreach Forum meets in conjunction with VICH Steering Committee meetings, which take place every nine months in one of the VICH member countries/regions. The Forum meetings are chaired by the VICH host country in collaboration with OIE, recognising the OIE's membership in VICH as well as its broader mandate.

OIE

Harmonising the regulatory systems to improve the availability of quality assured veterinary products is just one part of the jigsaw. True product availability is not achieved unless there is also a good infrastructure of veterinary services within a country, to distribute the products and to ensure they are correctly prescribed and used. This is where the OIE has a major role.

The OIE is the intergovernmental organisation responsible for improving animal health worldwide and is recognised as a reference organisation by the World Trade Organization (WTO). It plays a major role in two ways: firstly, by bringing international harmonisation through its worldwide reach – it has 181 member countries – and its activities setting international codes and standards; and secondly, through its activities in strengthening veterinary services, monitoring animal diseases, and setting standards on animal welfare.

The WTO members base their disease prevention and control measures on OIE's codes and manuals (both terrestrial and aquatic). Perhaps the best known of the OIE's missions is to improve knowledge of the global animal disease situation, including zoonoses, which it achieves through a unique tool, the OIE World Animal Health Information System, WAHIS.

Using its worldwide network of national experts, the OIE collects and analyses the latest scientific information on prevention and control of animal diseases, which is then made available to its member countries so that they can apply the most effective disease control methods. The experts are organised in national 'OIE Focal Points' and 'OIE Reference Centres'. The OIE helps its members to strengthen and improve the structure of their national animal health systems, particularly the national veterinary services, diagnostic laboratories and veterinary education. These support services are an essential part of a well-regulated and functioning market for veterinary medicinal products.

OIE also help developing and emerging countries deal effectively with health threats, by providing customised support within the framework of its PVS (Performance of Veterinary Services) Pathway.

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