

# Global Good Regulatory Practices and the New EU Regulation on Veterinary Medicinal Products

In 2018 a new regulatory-resource website was launched called *vetmed.world*, and in December a new section was published on that website called “Good Regulatory Practices”.

In January 2019 a new EU Regulation on veterinary medicinal products (VMPs) was published<sup>2</sup>.

What are the principles of good regulatory practice espoused by the *vetmed.world* website, and how does the new EU Regulation measure up?

## The International Interest in Good Regulatory Practices

The purpose of collecting examples from around the globe of good regulatory practice is to share ideas, solutions and approaches to regulatory issues; by learning from others, we aspire not to reinvent the wheel and to promote greater regulatory cooperation and convergence.

Regulatory authorities around the world are interested in sharing good regulatory practices as it helps them develop and evolve their own national systems, it fulfils their objectives of facilitating access to authorised medicines meeting the norms of quality, safety and efficacy, and it facilitates dialogue and mutual understanding at an international level. The latter point is important if countries are to cooperate in regional organisations or wish to undertake parallel or joint assessments of applications for marketing authorisation for VMPs. It helps if everybody speaks the ‘same language’ and has a common understanding of what a good regulatory system looks like. Efficiencies can be sought under the banners of “equivalence” (of regulatory systems) and “reliance” (of the regulatory work, assessments and decisions of trusted agencies).

This interest is being captured, at the international level, into a draft guideline on good regulatory practices for medicines currently under development by the WHO<sup>3</sup>.

Companies developing VMPs are interested in good regulatory practice because it allows them to operate in an efficient regulatory environment at a national or an international level.

The core regulatory principles that serve as the foundation for good regulatory practices include transparency, predictability, harmonisation, and a scientific risk-based approach to decision-making regarding quality, safety and efficacy. Companies look towards these principles to deliver regulatory environments where they can plan (predictable), where they know what must be done (transparent), where a balanced approach is taken to the risks and benefits of a product, and the investment is proportionate to their target markets.

Companies operating globally look towards good regulatory practice dialogue to:

(a) prevent regulatory systems in developed countries from organically growing into over-burdensome and

overly restrictive systems based on risk aversion, and remaining proportionate by being based on sound scientific evaluation balancing benefit and risk.

(b) bring the necessary regulatory framework for developing markets, particularly where insufficient regulatory control currently exists.

Companies also look towards regulatory pathways that foster innovation and new technologies, or products that meet unmet medical needs. These market-needs and long-term visions feed discussions in the evolving field of “Regulatory Science”.

Stakeholders, including veterinarians, also look towards good regulatory systems to improve the availability of needed veterinary treatments, such as being able to respond to emergency situations (e.g. a new pandemic disease), for example emergency or conditional approvals, or take a risk-based approach to the data requirements for low-risk products or niche markets (such as the “MUMS” scheme in the USA).

It is almost a law of nature that the small markets of the veterinary sector drive the need for a highly efficient regulatory system. A countering natural force is the evolution of expectations of consumers for improved safety, and demands of risk managers for expanding data sets. These ‘laws of nature’ provide the forces that drive all stakeholders, regulatory authorities and medicines developers, towards the regulatory efficiencies that can be gained by the process of international regulatory convergence. This is the gradual alignment of systems around the steady development and acceptance of international norms, through participation in harmonisation initiatives such as VICH, or international fora for regulators.

However, it is not just about having the right policies. It is also necessary to have the right institutions (adequately resourced), and the right tools (guidelines, staff, training, legal tools, etc.).

## Examples of Good Regulatory Practice

The *vetmed.world* website was set up using funding from the Bill and Melinda Gates Foundation and its tag-line “harmonising veterinary medicines registration” gives a clear indication of its purpose. The interest of the Gates Foundation is rooted in the importance of good governance in the regulation and control of VMPs and the part this plays in supporting socio-economic development as well as public health through better animal health.

The website covers the main elements of a regulatory system, from legislation, to marketing authorisation systems, manufacturing and market control. It provides a library of training materials, international guidelines, templates and examples to help set up a veterinary medicines regulatory system or to move towards regional harmonisation.

In the Good Practices section, examples of Good Regulatory Practice (GRP) from around the world are collected “for inspiration in the evolution of local regulatory

systems". There are more than 60 examples, divided into 12 categories.

In the first category are some of the bigger and broader 'initiatives', such as the WHO initiative to develop GRP guidelines, the APEC Regulatory convergence initiatives, and the World Bank project "Enabling the Business of Agriculture". The World Bank has identified the important elements that must be in place for a good regulatory system for VMPs. A selection of these are showcased in the Livestock chapter of the "Enabling the Business of Agriculture" 2017 report (see Table 1).

1.	There is both a regulatory framework requiring that all VMPs are registered (excluding emergency situations) and an institution actively registering VMPs.
2.	To limit delays in the registration process, dossiers are required to be checked for completeness prior to the start of an evaluation to ensure all required documents are included. The applicant is notified of the outcome of this validation process within a defined deadline.
3.	It should be explicitly stated what information must be submitted to obtain registration.
4.	The registration process should follow a fixed timeline, which this is published adhered to.
5.	An official list of all registered veterinary medicinal products in a country and their registration expiry date are publicly available. This registry of VMPs is easily accessible to the public.
6.	The packaging and labelling must provide a defined set of information with additional information, if necessary, provided in a package insert (information leaflet).
7.	Labelling requirements are comprehensive and provide distinction between what information is required to be on the outer and immediate package.
8.	Withdrawal periods are required on VMP labels for products for food-producing animals to protect consumers of foodstuff of animal origin.

Table 1: World Bank summary of key elements of a good regulatory system for veterinary medicines – adapted from World Bank "Enabling the Business of Agriculture" project reports

The World Bank EBA 2017 report also mentions that it should not be necessary to conduct a manual GMP inspection, as inspections should be done on a risk-based approach (i.e. only when deemed necessary). What is important is that a valid GMP certificate is included in all submitted applications for marketing authorisation. However periodic inspections of importers' storage facilities for imported product are recommended and the continuation of a business licence should be contingent on the passing of an inspection.

It is expected that additional examples of good regulatory practice will appear in the World Bank EBA 2019 report, including on pharmacovigilance systems.

The other 11 categories of Good Practice examples on the [vetmed.world](http://vetmed.world) website are:

1. **Pre-submission dialogue and activities:** such as good dialogue between the national regulators and interested parties and early pre-submission meetings for product development plans.
2. **Labelling and packaging:** such as multi-language packaging and dual labelling for two countries with a common language (e.g. UK-Ireland).
3. **Better Regulation:** such as drafting and implementation of new regulations and regulatory guidance in USA and

the Better Regulation initiative in EU (which is described in more detail below).

4. **Regulatory Science:** such as the European Medicine Agency's Regulatory Science Strategy initiative and the formation of expert groups on veterinary novel therapies and new technology.
5. **Shared evaluations and common procedures:** such as Regulatory Cooperation programmes (e.g. United States and Canada) and the Western Africa common registration process.
6. **Post-authorisation activities:** such as the variations guidance in the East African Community or the 'tell & do' variations system in the EU.
7. **Reducing administrative burden:** such as the use of master file systems for common parts of a dossier (e.g. manufacture of an active substance) so it can be submitted, assessed and registered separately; or the electronic application process at the regulatory agency in Australia (APVMA).
8. **Improving access to products and innovation:** such as conditional approval in urgent situations, or in 'exceptional circumstances', or for 'limited markets' (including 'minor species'), or initiatives to support innovation.
9. **Dialogue with stakeholders:** such as between applicant and assessor (e.g. UK), or oral hearings at the European Medicines Agency, or the Council to enable two-way communication in New Zealand.
10. **Operational transparency:** such as publication of fixed timelines for submission and evaluation of new product applications (EU), or publishing performance targets and outcomes (e.g. EMA and the Australian government Regulator Performance Framework).
11. **International alignment:** such as the VICH process for development of international guidelines.

#### Good Regulatory Practice in EU Law-making

In recent decades the EU law-making process has undergone major changes that have institutionalised Better Regulation<sup>4</sup>. This evolution began at the turn of the century (see Table 2) with (a) a codification process to bring together all the successive amendments to a piece of legislation into a single text (without changing the meaning); this brings more transparency to legislation that may be amended several times over a period of years; (b) an inter-institutional agreement on better law-making, leading to (c) an European Commission 'Better Regulation' initiative, which evolved later into 'Smart Regulation'.

In the following decade these founding initiatives led to the creation of a 'Better Regulation Package', in the form of a collection of tools and guidelines to support the EU decision-making in a process covering the entire policy cycle, and the "REFIT" programme (see Table 3). The aims were to ensure that (a) legislative initiatives are evidence-based; (b) there is transparent participation of all stakeholders; (c) unnecessary burdens for business and the public authorities are avoided; and (d) policies actually deliver as foreseen and remain fit for purpose.

An Impact Assessment Board (IAB), which was set up in 2006, enforced high quality standards for the impact assessments underpinning Commission proposals, earning the Commission excellent ratings in the 2015 OECD Regulatory Policy Outlook.

A big strength in the European system is the requirement for the European Commission to conduct impact assessments and stakeholder consultations prior to drafting major legislative proposals. But the biggest

Timeline	European initiatives towards Better Regulation
2001	Making regulations more transparent through "Codification of Community Acquis", Commission Communication 2001
2003	"Inter-Institutional Agreement on better law-making", European Parliament, European Council and European Commission, 31 Dec 2003
2003–2005	"Updating and simplifying the Community Acquis", Commission Communication 2003, leading to a strategy in 2005 and annual progress reports 2006–2009
2005	"Better Regulation for growth and jobs in the EU" Commission Communication March 2005, bringing in good regulatory practices, such as <ul style="list-style-type: none"> <li>• Impact assessments for all major new legislative proposals</li> <li>• Measuring administrative costs on industry – administrative cost model</li> <li>• Administrative cost-reduction targets of 25%</li> <li>• Guidance on choice of regulatory instrument; including reducing legislative initiatives and reliance on 'self-regulation'</li> <li>• More constructive dialogue with stakeholders</li> <li>• More focus on the application of EU community law to ensure it is correctly and fully implemented across all EU Member States</li> </ul>
2006	Impact Assessment Board was set up by the EC President on 14 November 2006
2010	"Europe 2020 – A Strategy for smart, sustainable and inclusive growth" Commission Communication March 2010
2010	"Smart Regulation in the EU" Commission Communication October 2010

Table 2 – How the EU Better Regulation programme evolved – the first decade

Timeline	European initiatives towards Better Regulation
2012	Regulatory Fitness and Performance Programme ("REFIT"): including REFIT Stakeholder Platform: C(2015) 3261 and REFIT Scoreboard: SWD(2015) 110
2015	European Commission Communication: Better regulation for better results – An EU agenda, COM(2015) 215, 19 May 2015
2015	Proposal for an Interinstitutional Agreement on Better Regulation: COM(2015) 216, 19 May 2015
2015	Better Regulation Toolbox (web-based), including Better Regulation Guideline: SWD(2015) 111
2016	Regulatory Scrutiny Board 1st year of activity, replacing the Impact Assessment Board, with a broader mandate to independently scrutinise the process in practice

Table 3 – How the EU Better Regulation programme was put into practice – the second decade

weakness in the system is that the European Parliament and the Council can make substantial changes to the Commission's legislative proposal without the need to evaluate the impact of their amendments.

### Good Regulatory Practice in the new EU Regulation on Veterinary Medicinal Products

With the adoption of the new EU Regulation<sup>2</sup> on VMPs it is worth reflecting on what elements of Good Regulatory Practice it encapsulates.

As described in the previous section, Good Regulatory Practice is in fact embedded in the process for the

development of EU legislation. The preparation for the drafting of the new VMP Regulation began in 2010 with an audit report on the current system, leading to a good definition of the objectives of the legislative review, followed by an impact assessment on the various legislative options, and a public consultation. The objectives included reducing the administrative burden created by EU legislation on both industry and public bodies, and more support for innovation in the animal health sector.

One good example of good practice in the final Regulation is the management of variations to a marketing authorisation dossier; the new VMP regulation takes their management one step further along the efficient administration road, by moving from a "tell & do" system for minor variations, to a "do & tell" system. In future, companies will be able to register minor changes (those defined as not requiring a scientific assessment) directly into an EU product database after the change has been implemented. This also reduces the administrative burden for regulators.

Another example aimed at reducing administrative burden, for both the regulator and the regulated, is the replacement of routine periodic reporting of a product's pharmacovigilance history, for example every three years, by a system of more continuous assessment based on an EU database for all pharmacovigilance reports coupled with a signal detection and signal management system.

An efficient system of variations to keep the marketing authorisation up-to-date, and an efficient system of pharmacovigilance, to ensure continual safety monitoring, has led to the deletion of the five-year renewal of marketing authorisations, as this is now considered obsolete. This illustrates a concept of Good Regulatory Practice whereby regulatory requirements, which may have built up over several decades, are reviewed and pared back to eliminate administrative tasks that do not contribute significantly to public safety and replace them with risk-based measures. This allows the regulator to see beyond the mounting pile of paper and focus resources where they will have most effect.

Information technology can be used in this way to support good regulatory practices to bring efficiencies and to hopefully reduce administrative burden. The new EU Regulation for VMPs includes a mandatory requirement to use electronic submissions, using a single standardised format, the use of interlinked databases covering all registered products, all GMP certificates and all pharmacovigilance reports, and an EU electronic prescription system. The latter will facilitate the collection of prescription and use data on VMPs.

### Conclusions

The sharing and understanding of Good Regulatory Practice fosters international regulatory convergence and brings efficiencies for both regulators and the regulated; this in turn supports the improved availability of authorised veterinary medicines and innovation; improved access to medicines has socio-economic benefits, particularly to agro-economies.

The EU Better Regulation programme has underpinned the recent review and updating of the EU legislation on veterinary medicines, such that it utilises many Good Regulatory Practices.



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