PEER REVIEWED

European Regulation 2019/6 on VMPs: Implications on Innovation

After a lengthy process of nearly 10 years, the new regulation on veterinary medicinal products (VMPs) has been published on January 8, 2019 to come into force on January 28, 2022. The new regulation constitutes of three parts: regulation 2019/4 on medicated feed, regulation 2019/5 amending regulation 726/2004 and regulation 2019/6 replacing directive 2001/82 as amended, both on VMPs. One of the major objectives of the new veterinary regulation was to foster innovation and thus this article will run through those articles that will influence innovation and thus the availability of VMPs in the EU.

Databases and Administrative Burden

The formal requirement for the establishment of a pan-European product database with all VMPs licensed in all Member States is a huge benefit for the market, but also for innovation, providing easier access to existing gaps and thus allowing innovators an improved basis for decision-taking. At the same time, the pharmacovigilance (PhV) database will be restricted, but opened to the public, which will allow third parties to innovate into safer medicines. While the first is seen as a fundamental improvement to the current system, the public access may also pose concerns. The new regulation will come into effect on 28 January 2022, and only regulatory procedures that start after this date, based on the application date, will be assessed under the new regulation and benefit from its rules. A number of new provisions reduce the administrative burden, which is certainly seen as beneficial and can support the innovation cycles. The "sunset" clause will not apply any more and products will therefore not need re-registration in the future, with the exception of MUMS. The pharmacovigilance system is regarded as appropriate to observe any potential risks after granting the marketing authorisation (MA). Improvements are implemented for pharmacovigilance (implementing the pharmacovigilance master file, omitting periodic safety update reports) and packaging and labelling, releasing workforce and financial resources hopefully to be used for innovation.

Supporting Innovation of New Products

True innovation is based on the possibility of allowing new technologies to enter the market. Recent examples show the need of the regulatory authorities to provide appropriate guidance to applicants who intend to obtain marketing authorisations for so called "novel therapies". The new regulation defines a "novel therapy VMP" as:

(a) a veterinary medicinal product specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy, phage therapy;
(b) a veterinary medicinal product issued from nanotechnologies; or
(c) any other therapy which is considered as a nascent field in veterinary medicine;

The first monoclonal antibody-based product (Cytopoint®) and stem cell-based product (ArtiCell forte®) were evaluated by EMA/CVMP and obtained positive opinions. Further technologies are considered to be licensed based on new technologies that may also not fit into the current scheme of pharmaceutical or immunological products. The new regulation allows for measures to keep track of the technical and medicinal development by giving the mandate to the EMA/CVMP 'executive director, in consultation with the CVMP, [to] set up the administrative structures and procedures allowing the development of advice for undertakings, particularly regarding the development of novel therapy veterinary medicinal products' (Art. 139). At the same time and based on this, 'the Commission shall adopt by the mean of delegated acts to Annex II of the regulation, to ensure legal certainty and harmonisation as well as any necessary updating, while avoiding unnecessary disruption with Annex II, including as regards the introduction of specific requirements for novel therapy veterinary medicinal products' (Art. 146).

A major step to improve the availability of VMPs and thus innovation are the extended data protection periods provided, especially for products intended for limited markets (MUMS), the equivalent to orphan drugs in human medicines: Table 1 compares the current and future protection periods. However, it is important to observe the reduced species (categories) that are defined as Major Species, as salmon and lactating sheep will fall under the definition of minor species (Table 2). This may encourage industry to invest into lactating sheep and salmon as these will be looking forward to benefit from the MUMS status when developing new products for these important, growing market.

Data protection	Directive 2001/82 as amended	Regulation 2019/9, effective for submissions from 28JAN2019, Art. 39
Additional data for existing products	---	Reduction of antimicrobial/-parasitic resistance or improvement of benefit/risk: 4 years
New product, 1 species	10 years	Major species: **10 years** **Minor species 14 years** (incl. salmon and dairy sheep)
Additional species	+ 1 year (only food-producing species)	+ 1 year per major species + 4 years per minor species
Fish and bees	13 years	Fish 14 years Bees 18 years
Antimicrobials	As other products	New active substance: 14 years
Maximum protection period	13 years (10 +3x1 year)	**18 years**
MRL	3 years, if any	**New species,** together with safety and residues tests and pre-clinical studies and clinical trials **: 5 years**

Table 1: Periods of the protection of technical documentation (Art. 39)

Directive EC 2011/82 as amended	Regulation EC 2019/06 Def. (29)
Cattle	Cattle
Sheep	Sheep for meat production
Pigs	Pigs
Chicken (incl. laying hens)	Chicken
Salmon	
Dogs	Dogs
Cats	Cats

Table 2: Definition of major species; all others are minor species

Limited markets and minor species
However, the definition of limited markets was slightly modified as compared to Directive 2001/82 (Table 3) (Art. 4 (29). Both subparts of the sentence appear pretty similar: low prevalence/incidence is replaced by "occurs infrequently", and limited geographic spread is now "in limited geographic areas". As this definition is especially relevant for minor diseases in major species, thus similar to orphan drugs in humans, it will be interesting to observe how EMA/CVMP will apply these terms. This may practically mean a restriction; it is further unclear how MUMS categorisations issued prior to 28 Jan 2022 will be used when the application for marketing authorisation for a "limited market" is submitted after this date.

Directive EC 2001/82 as amended	Reguation EC 2019/09 Def. (29)
Minor Species (=Non Major Species) or	Non Major Species or
Minor Use:	VMPs for the treatment or prevention of diseases
◂ Low prevalence/ incidence	◂ that occur infrequently or
◂ Limited geographic spread	◂ in limited geographic areas.

Table 3: Definition of limited market (previously MUMS)

A major advantage (and change from the current Dir 2001/82 EC) for products intended for limited markets is the implementation of an accelerated evaluation within 150 instead of 210 days within the centralised procedure (CP) for a VMP of major interest, particularly from the point of view of animal health and therapeutic innovation (Art. 44). Based on Article 23, in case of an application for a limited market (Table 3), the applicant shall not be required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the following conditions are met (Art. 4 (29)):

(a) the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided;
(b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.

Such MA for a limited market shall be valid for five years and either, based on a re-examination, be prolonged for further periods of five years or can be changed to an unlimited full MA when providing the missing information on safety and efficacy. This clause will be very beneficial for products intended for limited markets and, most probably, much more frequently used in the future, as more relevant than the option for an exceptional circumstances MA.

Definitions and Antimicrobials
Definitions (Art. 4 (15 and 16)) for the first time clearly define the terms "metaphylaxis" and "prevention" legally, which are of relevance especially for the development of antimicrobials (AM), but also have consequences for other products claiming such effects. Based on the topic of antimicrobial resistance (AMR), the development of any new antimicrobial product needed clarification, while the development of new substances (active ingredients) as antimicrobials remains challenging. Based on an implementing act, the Commission will have to present a list of those substances, which are

reserved for the treatment of humans (Art. 37 (5)). Any development of a new AM will require prior scientific advice with the competent authority, the EMA, being responsible for any MA for antimicrobials. The author doubts that this will encourage the development of new antimicrobial active substances, but it is regarded as a turn-around from the very negative attitude towards the use of antimicrobials as VMPs in the last years. Thus, new products may well be on the horizon as the uncertainty of the development of new antimicrobial products for animals, both pets and food-producing animals, consisting of known and non-critical antimicrobial substances, is de-risked via the scientific advice procedure and thus more attractive than previously.

Further clarifications are made to the definition (Art. 4) of an antimicrobial (any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals), antibiotic (any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases) and antiparasitic, meaning a substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity. The definition of an 'epidemiological unit' may aid in the differentiation

between vaccines requiring a marketing authorisation and those being inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit, or for the treatment of an animal or animals in a unit having a confirmed epidemiological link (Art. 2).

Although not with immediate effect, it is considered to foster innovation by evaluating and implementing reduced requirements for traditional herbal products (Art. 157). Similarly, the requirement posted to the Commission to evaluate the option to implement a 'monograph' system for the Environmental Risk Assessment (Art. 156) would reduce the financial burden and release more financial resources for innovation. However, new requirements for bioaccumulative and hazardous substances are rather discouraging for an investor.

Pre-clinical and Clinical Studies

A major component to develop innovative products is based on clinical studies. The regulation separates pre-clinical studies from clinical studies (Art. 4), the latter being defined as "a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof", while pre-clinical studies are thus all others. Test permits for clinical studies, to be conducted compliant to VICH Good Clinical Practice, are required and remain under the responsibility of national competent authorities, granted within 60 days from application. For the first time, it is explicitly defined that data stemming from clinical trials conducted outside the Union may be taken into consideration for the assessment of an application for a MA only if those trials were designed, implemented and reported in accordance with VICH GCP (Art. 9). While the initial proposal for the new regulation issued by the European Commission in 2014 refused to allow an exemption of Regulation 470/2009 for clinical trials, the final text of the regulation states that competent (national) authorities may set an appropriate (provisional) withdrawal time for clinical trials, an ultimate condition to support any development of VMPs for food-producing animals in the EU (Art. 9). Regretfully, even in the presence of appropriate residue data, this is restricted to clinical studies and thus not foreseen for pre-clinical studies, as this will require the euthanisation of animals. This appears to be against the recommendations of directive 2010/63, as long as no increased risk for the consumer exists. Interestingly, the introduction of the regulation requests to use the minimum number of animals for field studies (28), while such field studies are meant to generate efficacy and safety data in larger populations prior to registration. In summary, the administrative burden for the conduct of studies for the development of veterinary medicinal products rather increases considering the applications for test permits for pre-clinical and clinical studies, while rather more animals need to be euthanised and disposed of instead of being used based on risk evaluation for the consumer. Interestingly, the regulation seems not to apply for products tested for research and development including both, pre-clinical and clinical studies.

Medicated Feed

Regulation 2019/04 establishes the rules for medicated feed defined as '*feed, which is ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products or intermediate products with feed materials or compound feed*'. Medicated feed now includes the intended use of medicated feed for pets, containing immunological or pharmaceutical veterinary medicinal products. Such medicated feed will be prescription only and is not permitted, with the exception of veterinarians. Any organisation involved in the manufacturing up to the final distribution (feed business operators) must be registered based on an inspection. Current permissions of establishments falling within the scope of this regulation stay valid until 28 July 2022. Based on this regulation, it is expected that we will see increased innovation especially in the area of medicated feed for pets; it will be interesting to see if immunological products will also be developed as medicated feed. A provision for transporting test products (medicated feed) within the Union seems to be missing.

Conclusion

In summary, the new regulation represents clearly a step forward for those who wish to develop innovative veterinary medicinal products in the EU. Major improvements are present, especially for products intended for limiting markets. Further support for innovation cannot be judged now, as this may be dependent on the different delegated and implementing acts that need to be endorsed in the next years, first of all to Annex 2 of Regulation (EC) 2019/06, but also 24 other ones: A huge workload for those responsible and the interested parties who may need to give relevant input to achieve a workable final result.

Dr Klaus Hellmann

Dr Klaus Hellmann is a veterinarian with more than 25 years' experience in the animal health industry. Prior to founding Klifovet in 1997 as a CRO, he worked in veterinary practice, academia and the animal health industry. He is a board-certified veterinary pharmacologist, Diplomate of the European College of Veterinary Pharmacology and Toxicology, and holds the title of an Auditor (European Organisation of Quality). As CEO of Klifovet, he acts as consultant on international VMP product development.

Email: klaus.hellmann@klifovet.com

Dr Regina Wolf

Dr Regina Wolf is a veterinarian with over 14 years' experience in the pharmaceutical industry. She was CRA for human clinical trials and manager for veterinary trials for EU development. Before she joined Klifovet AG as Head of Product Development, she was Assessor for Immunologicals at the Veterinary Medicines Directorate, UK. She is now heading the regulatory affairs unit at Klifovet AG.

Email: regina.wolf@klifovet.com