Animal Pharm
Agribusiness intelligence

The new veterinary medicines regulation: What we know and what we don't

by Dr Karolina Bate

Cyton Biosciences
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Dr Karolina Bate, managing director at Cyton Biosciences casts her eye over what will be the biggest changes to European veterinary regulation this decade. What has already been decided and what will be subject to further discussion?

On January 7, 2019, Regulation (EU) 2019/6 on Veterinary Medicinal Products (VMPs) was published in the Official Journal of the European Union, which repeals Directive 2001/82/EC. During the many years of development of this legislation, it has come to be referred to as the Veterinary Medicines Regulation, or simply the VMR, and it will apply from January 28, 2022.

The first of this two-part series of articles – 'The evolving regulation of veterinary medicines in Europe: Progress or bureaucracy?' – puts the VMR in context. This is just the latest step in the continual refinement of the legislation governing VMPs in Europe.

This important milestone has been reached following years of consultation and negotiation, which officially started with the European Commission's initial proposal – published back in September 2014. However, there is still a long way to go, with much of the important detail to be defined in implementing and delegated acts, which have not yet been written. As recently stated by member of European Parliament Fredrick Federley: "This is when the real work begins."

This overview is arranged to reflect the structure of the VMR, with subjects organised under the relevant chapter headings, focusing on areas where there will be the most significant changes with respect to product development and regulatory affairs (chapters I-IV and chapter VI). This article will not discuss the new Regulation on Medicated Feed (2019/4).

The full VMR, as published in the Official Journal, can be found here.

Chapter I: Subject matter, scope and definitions

Known Changes

Autogenous vaccines included in scope

Separate definitions for antibiotics, antimicrobials and antiparasitics, as well as definitions of prophylaxis and metaphylaxis

Implementing acts required

Article 3.2 – Decisions on classification of products as VMPs

Generally, there are no surprises in this first chapter but whereas autogenous vaccines were not mentioned in Directive 2001/82, they have been included within the scope of the VMR.

In addition, it should be noted there was extensive discussion regarding the definitions used in the VMR, particularly those relating to antimicrobial resistance (AMR), with the result being separate definitions for antibiotics, antimicrobials and antiparasitics, as well as definitions of prophylaxis and metaphylaxis.

The discussions have essentially been concluded in this Chapter and the only scope for a further update is the option under Article 3(2), which is for the Commission to adopt implementing acts on whether a specific product or group of products is to be considered as a VMP.

Chapter II: Marketing authorisations – general provisions and rules on applications

The general provisions and rules for marketing authorisation (MA) applications will see quite a range of changes as summarised in the boxes at the beginning of each section and elaborated in the text below.

Section 1 – General provisions

Known Changes

MA valid for unlimited period (no renewal, no sunset clause)

Additional acts required

None

One of the very few simple 'wins' for industry has been the deletion of renewals and the sunset clause in the VMR; MAs will be valid for an unlimited period and there will be no risk of the MA lapsing in situations where the product has not been marketed for a long period of time (the 'sunset clause').

The exception to this is MAs for limited markets (see Section 6), which will be valid for five years and can be renewed repeatedly for as long as they remain classified as being for a limited market.

Section 2 – Dossier requirements

Known Changes

Pharmacovigilance (PV) master file

AMR risk assessment and risk mitigation proposal

Additional acts required

None

Chapter IV discusses the changes in requirements for PV in greater detail but a significant change is the introduction of the PV master file, for which a summary will need to be presented in the MA application dossier.

Section 2 of Chapter II also introduces the first of the new requirements for antimicrobial VMPs, adding the need for an antimicrobial risk assessment and AMR risk mitigation proposal to be included in the MA application dossier.

Section 3 – Clinical Trials

Known Changes

Entirely new section: new harmonised EU requirements for trial licence applications

Additional acts required

None

Previously, the procedure for applying for permission to carry out a clinical trial for a VMP was regulated entirely at national level but the VMR introduces some degree of EU harmonisation.

The details of what is required to obtain a trial approval remains largely regulated at a national level but there are now specified timelines for the decision to grant or refuse a clinical trial approval.

Section 4 – Labelling and package leaflet

Known Changes
Provision for pictograms, standard abbreviations and national identification code

Implementing acts required
Article 17(1) – Identification code to go on immediate packaging

Article 17(2) – Abbreviations and pictograms

Article 17(3) – Packaging unit size for small packages

The new rules for labelling will allow for reduced text, taking further the current initiatives for the use of pictograms and abbreviations. This is of importance for multilingual packs, where a single pictogram or abbreviation will be able to replace text in several languages. Member States will also be allowed to request the addition of a national identification code to the immediate and outer packaging.

- Three implementing acts will be required to confirm the final details of Section 4:
- Rules will be decided for the national identification codes to go on packaging;
- A list of approved abbreviations and pictograms will be agreed; and
- Rules on "small immediate packaging" that is too small to contain the usual information required on immediate packaging will be confirmed.

Section 5 – Specific requirements for generics, hybrid and combination VMPs and for applications based on informed consent and bibliographic data

Known Changes
No significant changes

Additional acts required
None

Section 6 – MAs for limited market and in exceptional circumstances

Known Changes
MAs for limited markets valid for five years, multiple renewals possible

Delegated acts required
Article 37(4) – Criteria for designation of antimicrobials to list as reserved for use in humans

Implementing acts required
Article 37(5) – List of antimicrobials reserved for use in humans

Environmental impact was an area of considerable discussion throughout the drafting of the text of the VMR but overall, industry has avoided the worst of the possible increases in requirements – for the moment. Environmental impact is revisited in various other Chapters (see Chapter IV, section IV and Chapter XII) but for Chapter II the main change is there is now the possibility for a MA to be refused if the VMP contains a PBT active substance.

This is not a complete ban and PBTs can be used if the benefit-risk assessment is acceptable. However, as discussed in Chapter XII, there will be further discussion of a possible active substance-based review system (monographs) for environmental risk assessments (ERAs).

The other major additions to the possible reasons for refusal to grant a MA are if an antimicrobial VMP is an antimicrobial reserved for treatment of certain human infections and if the risk of development of antimicrobial or antiparasitic resistance outweighs the benefit. A delegated act is required to determine the criteria for designating antimicrobials to the reserved list and a further implementing act is required to create the actual list of reserved antimicrobials. These two acts will have very important implications for industry and for the future treatment of infectious diseases in animals.

Section 8 - Protection of Technical Documentation

Known Changes
Extensive revision of protection periods

Additional acts required
None

The data protection periods, now referred to as 'periods for protection of technical documentation' (to avoid confusion with data protection relating to individuals), have been significantly revised to promote innovation but the concept of the global marketing authorisation remains. The new periods of protection can be summarised as follows:

- The protection period for the first MA for a major species remains at 10 years;
- For minor species this is increased to 14 years or 18 years in the case of products for bees;
- New antimicrobials also have a protection period of 14 years;
- Adding additional species to a MA, either in the initial MA or in an extension procedure increases the protection period by one year per major species and by four years per minor species, to a maximum of 18 years;
- Sponsorship of new maximum residue limits (MRLs) will result in an additional five years protection; and
- Old products (where all previous periods of protection have lapsed) for which new data supports a reduction in antimicrobial or antiparasitic resistance, or supports an improved benefit-risk balance, will receive four years protection for the new data.

Chapter III: Procedures for marketing authorisations

There have not been the sweeping changes made to the procedures for MAs that industry had pushed for, where it was hoped that there could be a simple system of one application – one assessment – one authorisation (1-1-1) throughout Europe. The national marketing authorisation procedure has been retained and, therefore, the need for the mutual recognition procedure (MRP) and decentralised procedure (DCP) are also retained.

However, in a step closer to the 1-1-1 goal, the centralised procedure (CP) will be open to any application for which an MA has not previously been granted in the EU (through the NP, MRP or DCP).

In a further disappointment to industry, the initial wording of the Regulation proposed by the EC, where voting by The Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv) was going to be by majority, has reverted to a consensus voting system. The EC will be required to issue the final decision, when the CMDv cannot reach consensus, in the review procedure outlined in Section 6.

Critically, whenever the EC needs clarification from the national competent authorities or the European Medicines Agency before a decision can be made (which is likely to be fairly routine), there are no timelines specified for this clarification phase, so the review procedure could be prone to delays.

Section 1 – MAs valid throughout the EU (Centralised MAs; CP)

Known Changes

CP will be open to all MA applications

Additional acts required

None

Section 2 – MAs valid in a single member state (National MAs; NP)

Known Changes

No significant changes

Additional acts required

None

Section 3 – MAs valid in several member states (Decentralised MAs; DCP)

Known Changes

No significant changes

Additional acts required

None

Section 4 – Mutual recognition of national MAs (MRP)

Known Changes
No significant changes

Additional acts required
None

Section 5 – Subsequent recognition in the MRP and DCP

Known Changes
No significant changes

Additional acts required
None

Section 6 – Review Procedure

Known Changes
Consensus voting by the CMDv is retained with the EC responsible for arbitration when the CMDv does not reach consensus

Where the EC seeks advice from the NCAs or the EMA during arbitration, no timeline is specified

Additional acts required
None

Chapter IV: Post-marketing authorisation measures

Section 1 – Union product database

Known Changes
Introduction of the need for a single VMP database to record authorisation details and marketing status

Additional acts required
Article 55(3) – Union product database specifications

The introduction of the union product database, which will contain details of all EU MAs for VMPs, including those authorised at a national level, was a key requirement to the much-welcomed deletion of renewals and the sunset clause (see Chapter II). The database will be 'interconnected' with the pharmacovigilance database (see Section 5) and the manufacturing and wholesale distribution database (see Chapter VI).

However, aside from the basic details which must be included in the database, as specified in the VMR, implementing acts are required to determine what other information will be included in the database and all the detailed specifications of how the database will accessed, who will have access and updating responsibilities etc.

Section 2 – Collection of data by member states and responsibilities of Marketing Authorisation Holders (MAHs)

Known Changes
Obligations on all EU MS to collect data on the sales and use of antimicrobials, with support from the MAHs

Delegated acts required
Article 57(3) – Rules of methods for collection of use data on AMs

Implementing acts required
Article 57(4) – Format and requirements for collected AM data

Although there are many national initiatives already in place for the collection of data on the sales and use of antimicrobials, the VMR puts this data collection into European legislation and will bring all the European data together for analysis by the EMA, in a further increase in requirements relating to the fight against AMR. A delegated act and an implementing act will be required to clarify various details including for which types of antimicrobials data will be required.

Section 3 – Changes to the terms of the MA (Variations)

Known Changes
Closed list of Type 1 variations (no Type 1a/b)

Implementing acts required
Article 60(1) – List of variations not requiring assessment

Article 65(4) – Work sharing procedure for variations

Another major change is the move from three variations categories (Type 1a, Type 1b and Type 2) to two categories; under the VMR there will 'simply' be variations that do not require assessment and those which do.

Unfortunately, industry was not successful in getting a closed list of variations requiring assessment, so the default in the case that a variation is not listed, will be for the variation to require assessment. An implementing act will be required to create the list of variations not requiring assessment, but it is not yet clear how this 'yes or no' classification system will deal with the complexity of variations.

As explained in the previous article in this series, many years of refinement has resulted in the current regulatory framework and the current variation classification guideline is a good example of how the legislation has adapted to the needs of industry and the regulators. There is a danger that, in an attempt to simplify the legislation, industry will lose important clarity. Further implementing acts may be put in place to make the necessary arrangements for variation work sharing procedures.

Section 4 – Harmonisation of the Summary of Product Characteristics (SPCs) for national MAs

Known Changes
Brand new concept for the regulation of VMPs

Reference products with disharmonised SPCs will be harmonised first, with no re-assessment, followed by the generics of those reference products

VMPs authorised before October 2005 and which have not yet had an ERA carried out, will not be eligible for the harmonisation procedure until an updated ERA has been carried out

Additional acts required
None

The final text of this section, which represents an entirely new feature in the VMR, shows an important victory for industry, because the harmonisation of SPCs will not be carried out at the level of groups of products with the same active substance or in the same class; the harmonisation will be limited to groups of the same products with the same MAH, with disharmonised SPCs across different member states; it focuses on harmonisation of individual companies' own collections of disharmonised national SPCs, where products were authorised before the introduction of the MRP.

The reference products will be harmonised first, according to an annual list drawn up by the CMDv. Once the harmonisation procedure for the reference product is closed, the generics (and hybrids) which are based on the reference product will have 60 days to apply for the harmonisation of their corresponding SPCs.

The list of SPCs drawn up by the CMDv will not be able to include any VMPs authorised before October 2005 and for which there has not been an ERA carried out; those products will need to have an ERA carried out before any harmonisation can take place. It is not yet clear how quickly and by what method these requests for absent ERAs will be taken forward.

Section 5 – Pharmacovigilance

Known Changes
No Periodic Safety Update Reports (PSURs)

No Detailed Description of the PV System (DDPS)

All Adverse Events (AEs), serious and non-serious, to be submitted within 30 days

Introduction of the PV system master file

Increased focus on signal management

Additional acts required
Article 77(6) – Good PV practices and PV System Master File

Probably the most extensive update in requirements is in the PV section of the VMR, which sees a move towards continual safety monitoring instead of periodic safety review. The DDPS, which at present must be submitted with every MA application is replaced with a summary of the newly introduced PV system master file.

In addition, PSURs will no longer be required, shifting the focus instead to continual signal management. Reporting by the MAH will only be required when there is a change in the benefit-risk balance. There will also be a notable change in spontaneous AE reporting: non-serious AEs which were previously only reported in PSURs will now need to be reported to the PV database within 30 days, which is the same as the new reporting timelines for serious AEs.

It is hoped that these changes will reduce administrative burden for both industry and the regulators, but the details of the implementing act to specify the requirements for Good PV Practice (including what is expected in terms of signal management) and the PV system master file will be critical.

It should also be noted that many of the PV obligations are now listed in Annex III, for which financial penalties will be imposed by the Commission, where MAHs fail to meet with these obligations – highlighting the increased importance being placed on PV systems. This is not unexpected, considering the regulators will no longer be routinely provided with updates in the form of renewals or PSURs.

Section 6 – Union interest referral

Known Changes
No significant changes

Additional acts required
None

Chapter V: Homeopathic VMPs

Known Changes
No significant changes

Additional acts required
None

Chapter VI: Manufacturing, import and export

Known Changes
Introduction of separate legal basis for veterinary GMP, relating to products and active substances

Database on manufacturing and wholesale distribution linked to the Union Product Database

Mandatory inspections of new manufacturing sites

Additional obligations relating to active substances; introduction of GDP for active substances

Tightening of qualifications required for QP for batch release

Implementing acts required
Article 93(2) – GMP for VMPs and active substances

Article 95(8) – Good Distribution Practice for active substances

Chapter VI is another area where there are quite significant changes and significant unknowns. There has essentially been a complete re-write compared to the equivalent Title IV of the current legislation (Directive 2001/82/EC, as amended) and although the overall meaning is unchanged, there are numerous subtle changes which will have an impact on the requirements being made of industry and regulators.

These changes are summarised in a very general level in the box above but probably most significant of all is the introduction of a new legal basis for veterinary GMP, which is no longer common to the legal basis of GMP for medicinal products and actives substances for human use.

Clearly, it is in the interests of both the regulators and industry to remain as closely aligned as possible to the human GMP regulations; strong representation from all stakeholders in the animal health sector will be essential during the consultation process for the Implementing Acts for veterinary GMP and GDP for active substances.

The other major change will be that a database on manufacturing and wholesale distribution will be established. This will be linked to the Union Product Database (see Chapter IV, Section 1) and it will also be central to all the other requirements introduced in Chapter VI, being the central repository of relevant information for the competent authorities to refer to.

Chapter VII: Supply and use
This Chapter moves on from product development and regulatory affairs into distribution and use, which are not the focus of this article. Therefore, below is simply a summary of those areas where there are further legislative acts required.

Section 1 - Wholesale distribution

Implementing acts required
Article 99(6) – Good Distribution Practice for VMPs

Section 2 - Retail

Implementing acts required
Article 104(7) – Design of common logo for sales by distance (internet)

Section 3 - Use

Delegated acts required
Article 106(6) – Measures for safe oral administration to food animals

Article 109(1) – Passport for non-food producing equines (content & format)

Article 115(3) – Rules on withdrawal periods in the light of new science

Article 118(2) – Import of animals treated with antimicrobials in 3rd countries

Implementing acts required
Article 105(8) – Model format for veterinary prescription

Article 107(6) – List of antimicrobials forbidden for cascade use

Article 109(2) – Passport for non-food producing equines (model forms)

Article 114(3) – Substances essential for food producing aquatic animals

Article 115(5) – List of substances essential for equines

Section 4 - Advertising

Additional acts required
None

Chapter VIII: Inspections and controls

Known Changes
No significant changes

Additional acts required
None

Chapter IX: Restrictions and penalties

Known Changes
Introduction of financial penalties

Delegated acts required
Article 136(7) – Financial penalties imposed by the Commission

Chapter X: Regulatory network

Known Changes
No significant changes

Delegated acts required
None

Chapter XI: Common and procedural provisions

Known Changes
No significant changes

Delegated acts required
Article 146(1) and 146(2) – amendments to Annex II (dossier requirements)

At present Annex II of the VMR is a copy of Annex I from Directive 2001/82, which includes both the administrative (Part 1) and the technical requirements (Parts 2, 3 and 4) for inclusion in the MA application dossier. In accordance with the delegated acts, the administrative information will be separated out into Annex I of the VMR and Annex II of the VMR will be updated to retain only the technical information. The delegated acts will also introduce the necessary changes to add all the new requirements specified throughout the rest of the VMR.

Chapter XII: Transitional and final provisions

Additional acts required

Article 156 – Feasibility study of an active substance-based review system (monographs) for ERAs

Article 157 – Commission report on traditional herbal products used to treat animals

Article 158 – Review of measures regarding animals of the equine species [and their exclusion from the food chain]

The final Chapter specifies the timelines for the adoption of the various delegated and implementing acts, which are mostly scheduled to also apply from January 2022, so the complete VMR and all the delegated acts will apply from the same date.

The other important 'unknown' introduced in this final Chapter is the Commission's feasibility study on the possibility of a monograph system for ERAs (and other potential alternatives). This leaves the discussion on ERAs for VMPs firmly open.

Conclusion

This article has summarised at a very high level the changes which we know will come with the VMR and highlights where there are further details which are as yet unknown.

Even looking at these changes in the simplest terms is not a brief exercise and gives an indication of just how much impact these changes will have on the development and regulation of VMPs.

With a further 28 delegated and implementing acts to be written and three reports to come from the Commission, to repeat the words of Fredrick Federley quoted at the beginning of this article: "This is when the real work begins."

The clock to January 2022 is ticking.