Proposals to Annex 2 of the European Regulation 2019/6 on VMPs

With the support of the EMA/CVMP, the European Commission appears well on track with the process of drafting the delegated act (Art. 146) on Annex II of the Regulation (EU) 2019/6[1]. It appears that Annex II is well progressed and may be finalised earlier than the deadline set for 28 Jan. 2022. The scientific recommendations provided by EMA/CVMP on Annex II[2] will require a variety of further guidance documents, which need to be adapted or created; however, the current version of the proposal allows flexibility and room for maneouvre for both regulators and industry to adapt to new approaches for the development of new and innovative products. While the structure of the Annex II, Title I, Title IIb and Title III.1 to III.7 are more or less identical to the previous Directive 2009/9, the contents of Title IIa, Title III.8 and IV define new specific requirements to obtain marketing authorisations for non-immunological biological veterinary medicinal products (VMPs), novel therapies and provide more detail on particular veterinary medicinal products.

Introduction

The status of the "Scientific recommendations on the revision of Annex II to Regulation EU 2019/6" issued by EMA/CVMP on 18 July 2019[2] has been circulated to the council members without much change (internal communication of author) by the European Commission (EC). As a draft was not published by the EC at the time this article was written, the authors used the cited document[2] as the basis for this article. The basic structure of Annex II is displayed in Table 1.

As indicated by CVMP in their initial consideration and rationale to modify the previous Annex 1 of Directive 2001/82 in the form of Annex II of the new regulation, the guidance regarding the technical requirements on the quality, safety and efficacy of VMPs worked sufficiently well in practice before. It did and does assure a sufficient level of detail to ensure legal certainty and harmonisation, but it is considered necessary to adjust in order to respond to identified discrepancies in the international scientific progress or latest developments including guidance from VICH, WHO and OECD. There is a mandate to avoid major changes[2].

The marketing authorisations in Europe will be granted based on Article 8, or 18 to 25 for any VMP where a dossier is submitted on or later than 28 January 2022. Such a dossier has to follow Volume 6B, all other applicable parts of the Notice to Applicants[3], and the requirements for electronic format (VNeeS) when submitting documents as published by the agency and making such documents legally binding. Also binding in the generation of data for a product's marketing authorisation application are the current state of veterinary medicinal knowledge, the scientific guidelines related to quality, safety and efficacy of VMPs as published by CVMP, the monographs of the Eur.Ph., GMP, OECD-GLP, and VICH-GCP standards, the application of animal welfare based on Directive 2010/63/EC in all studies submitted, and where applicable, Directive 2001/18/EC in case of release of VMPs containing genetically modified organisms (GMOs). The EMA-CVMP proposal makes reference to Art. 34[3], allowing an applicant to apply for a status of "not subject to veterinary prescription" together with the MAA dossier. Such an application should follow the legal requirements outlined in Art 34 (3 a-g) of the Regulation, including a critical review of the safety profile aimed to justify the suitability of such classification[2].

Overview

While Title I remains primarily unchanged (minor updates to the technical requirements to VMPs other than biological VMPs), the major structural difference is in Title II, now covering all kinds of biological products. Title IIb represents an update to the technical requirements to immunological VMPs very similar to Title II of Directive 2009/9/EC. Title IIa defines for the first time the technical requirements for biologial VMPs not exerting an immunological action, covering a product category that has experienced increasing attention in veterinary medicine over the past years.

The specific marketing authorisation applications (MAA) in Title III underwent a set of changes: the paragraphs on similar biological VMPs and mixed MAA categories were deleted while the well-established use may be covered by 'applications based on bibliographic data' or covered by other applications. As shown in Table 2, specific requirements for hybrid applications, limited markets and novel therapies were defined.

In Title IV, the specific chapter on homeopathic VMPs has been deleted while the requirements on immunological VMPs has been extended. More detailed requirements are proposed to be added to both in the form of the vaccine antigen master file as well as the multi-strain-dossier and the concept of a vaccine platform technology. All of these are valuable changes and tools for applicants seeking marketing authorisations for new innovative technologies.
The structure of the dossier, independent of the product category, remains unchanged with Parts 1, 2, 3 and 4 reflecting the summary of the dossier (administrative part), the physicochemical, biological and microbiological information (quality), safety and residue tests (safety) and pre-clinical and clinical trial(s) (efficacy). Critical expert reports are further required on all parts of the dossier, while the detailed description of the pharmacovigilance system (DDPS) will be replaced by a pharmacovigilance master file, that needs to be defined in a separate implementing act based on Art. 77[6].

Title IIa: Requirements for Biological VMPs other than Immunologicals

This new part of the Annex II is specifically dedicated to biological VMPs without immunological action. It follows the well-known principles, structure and headers as already known from Title I and II of Directive 2009/9/EC. Beyond all the criteria applicable for any VMP, specific attention is required based on the characteristics of the biotechnological or biological substance, its microbiological characteristics, potential impurities and contaminations, and the source and definition of the starting materials, during the manufacturing process to the final product. The qualitative and quantitative composition must be well defined and biological activity per unit should be indicated.

Title	Regulation (EU) 2019/6: Annex II	Specific focus on:
III.8	**Applications for novel therapies**	Nascent field of VMPs: seek advice at the agency
8.1.	General Requirements	Apply risk profiling for risk analysis and management
	8.1.1 Requirements regarding quality	Take care of potency assay for biological VMPs
	8.1.2 Requirements regarding safety	Specific risk in cases of GMO
	8.1.3 Requirements regarding efficacy	Indications claimed must be supported by data in target species
8.2.	Specific data requirements	Evaluate case-by-case with specific detail required for:
	8.2.1 Gene therapy VMPs	Starting materials, quality and safety
	8.2.2 Products for regenerative medicine, tissue engineering and cell therapy veterinary medicinal products	Starting materials, quality and safety
	8.2.3 VMPs specifically designed for phage therapy	Starting materials, quality and safety
	8.2.4 VMPs issued from nanotechnologies	Starting materials, quality and safety
	8.2.5 RNA antisense therapy and RNA interference therapy products	Starting materials, quality and safety

Applications for Novel Therapies

Method descriptions and validation of release tests, including potency tests, are obligatory; validated biological assays may be used when physicochemical methods are not sufficient. Sterility, batch-to-batch consistency and stability have to be proven. Safety and efficacy testing follow the principles as established for pharmaceutical products.

Title III.1–7

As indicated in Table 2, specific marketing authorisations are defined for three new kinds of applications: hybrid applications, applications intended for limited markets and for novel therapies. At the same time, the so-called biosimilars are not mentioned any more and no mention of mixed applications has survived. Most of these will fall under other categories of applications (e.g. generics, hybrids, informed consent) as the well-established use (e.g. bibliographic data). Hybrid applications have increased during the last decade and it appears logical that these are mentioned in the Annex now.

For applications for limited markets, Article 23 of the regulation 2019/6 clearly stipulates that, in the "absence of comprehensive safety and/or efficacy data the applicant can demonstrate that the product is intended for use in a limited market and that the benefit of availability of the new product outweighs the risk associated with the omission of some of the safety or efficacy data required by this annex", an MA shall be granted. The Annex makes reference to the current MUMS guidelines, but the definition of the regulation appears to go beyond the current MUMS requirements for minimum safety and efficacy data. The MUMS guideline on safety is currently under review and stakeholders are asked for their comments in early 2020.

Title III.8: Requirements for Novel Therapies

For all those interested in new innovative products, the most exciting part of the future Annex II appears to be the part on novel therapies including those therapies still nascent, thus unknown. In order to allow for a high level of flexibility, the approach described mainly focuses on a risk evaluation of such new technology and therapy, while best managing and controlling such risks to be able to conclude on a positive benefit:risk balance, the basis for the granting of a marketing authorisation in Europe. A thorough risk profiling methodology must be applied to identify all inherent risks and contributing factors and to be able to control them efficiently. In many cases, advice from the competent authorities will be highly recommendable to run an efficient product development programme. Table 3 lists the different types of novel therapies currently defined and provides a hint to the potential major additional areas of focus that should be applied. Depending on the nature of the product (biological, non-biological, immunological, non-immunological), another part of the Annex II (Title I, Title IIa or Title IIb) will have to be followed, allowing for some flexibility, if justified. While there are five types of novel therapies mentioned (Table 3), only one product has been registered in Europe until the end of 2019 falling within the scope of these categories; it is the first stem cell-based product Arti-Cell® Forte, GST, Belgium[4]. It will be interesting to observe if the goal of the EC fostering innovation will be confirmed by new technologies reaching the market with the implementation of Annex II. It is anticipated that further guidance will be appreciated by applicants to de-risk the development process of their innovative technologies and products as VMPs.

Title IV: Requirements for MAAs for Particular VMPs

While the proposal provides a clearer definition and more detailed advice on the requirements of vaccines where a vaccine antigen master file may be applicable, it also provides further confirmation on the evaluation and certification of such a master file. As any certificate issued shall apply throughout the European Union, this supports the harmonised approach and values the effort.

The multi-strain dossier has been opened to all inactivated vaccines against antigenically variable viruses, where a rapid and frequent change in the composition of the vaccine formulation is needed to ensure efficacy with regard to the epidemiological situation in the territory of use. Each multi-strain dossier is applicable only to one virus species. It clearly mentions that, based on the epidemiological situation where the vaccine is intended to be used, a number of strains could be selected from those included in the dossier to formulate a final product. It will be interesting if this approach will also be applicable for other technologies, e.g. phage therapy.

The new chapter on vaccine platform technology first of all gives a definition: Vaccine platform technology is a collection of technologies that have in common the use of a 'backbone' carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform. This includes, but may not be limited to, protein-based

Titles	Directive 2009/9/EC)	Parts	Titles	Regulation (EU) 2019/6: Annex II	Parts
Title I	VMPs other than **immunological** VMPs	1 to 4	Title I	VMPs other than **biological** VMPs	1 to 4
Title II			Title II	Biological VMPs	
			Title II a	Biologicals other than immunological VMPs	1 to 4
	Immunological VMPs: Part 1 to 6	1 to 6	Title II b	Immunological VMPs	1 to 5
Title III	Specific Marketing Authorisation Applications	7 options	Title III	Specific Marketing Authorisation Applications	8 options, see table 2
Title IV	MAA for particular VMPs	1. Immunological VMPs;	Title IV	MAA for particular VMPs	1. Antigen Master File;
					2. Multi-strain dossier;
		2. Homeopathic VMPs			3. Vaccine platform technology

Comparison of Product Categories

Title III	Directive 2009/9/EC)	Based on/ Reference to
1	Generic VMPs	Art. 13
2	Similar biological VMPs	Art. 13 (4)
3	Well-established veterinary use	Art. 13 (a)
4	Combination VMPs	Art. 13 (b)
5	Informed consent applications	Art. 13 (c)
6	Exceptional circumstances	Art. 26 (3)
7	Mixed MAA	Case-by-case

Title III	Regulation (EU) 2019/6: Annex II	Based on/ Reference to
1	Generic VMPs	Art. 18
2	Hybrid applications	Art. 19
3	Combination VMPs	Art. 20
4	Applications based on Informed consent	Art. 21
5	Applications based on bibliographic data	Art. 22
6	Applications based for limited markets	Art. 23
7	Applications in exceptional circumstances	Art. 25
8	Applications for novel therapies: see table 3	Definition: Art. 4 (43)

Comparison of Specific MAs

platforms (virus-like particles), DNA vaccine platforms, mRNA-based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines. Such applications are eligible for reduced data requirements, after a full dossier has been provided for the first product based on the technology. A 'platform technology master file' comprising all data relative to the platform, for which there is reasonable scientific certainty that it will remain unchanged regardless of the antigen(s)/gene(s) of interest, may be submitted with the first full dossier based on the platform technology. A positive evaluation shall result in a certificate of compliance to the European legislation for the platform technology master file, which shall apply throughout the Union.

Does Annex 2 meet the objective? Not surprisingly, there are topics appreciated and others criticised. While in principle, innovation is supported by a couple of measures in the Regulation, the administrative burden certainly has rather increased. Reasons for this are provided by the industry, Animal Health Europe, and EGGVP who provided their view on the proposal[5] which is recommended to those interested.

Conclusion

In summary, the advice given by EMA/CVMP in the form of the scientific recommendation on the revision of Annex II meets the vast majority of expectations of interested stakeholders and it appears likely that the European Commission, after consultation with the Council, will use most of the proposals for the final version. It will be more than welcome if Annex II will be finalised well in time to allow applicants to follow it when submitting MAA after 28 January 2022. While the regulation stresses the importance of benefit:risk evaluation when granting MA, Annex II puts even more focus on a detailed benefit:risk evaluation of all aspects of new products; especially for novel therapies, a risk profiling methodology to identify all risks inherent to a specific product and the risk factors contributing to those risks are fundamental to a successful MAA. This will be the basis and may allow future new innovative technologies to obtain market access in Europe, even in the absence of specific mention in the current Annex II.

REFERENCES

1. Regulation (EU) 2019/6 of the European Parliament and of the council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
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3. The rules governing medicinal products in the European Union, Volume 6 B, Notice to applicants, Veterinary medicinal products, Presentation and Contents of the Dossier
4. Arti-Cell Forte, Summary of opinion: https://www.ema.europa.eu/en/documents/smop-initial/cvmp-summary-positive-opinion-arti-cell-forte_en.pdf
5. Comments by stakeholders on the "Scientific recommendation on the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products", https://ec.europa.eu/food/animals/health/veterinary-medicines-and-medicated-feed/imp-regs-2019_en

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