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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on a feasibility study of an active-substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products

1. INTRODUCTION

This report delivers on the obligation of the Commission pursuant to Article 156 of Regulation (EU) 2019/6 of the European Parliament and of the Council[1] to present the findings of a feasibility study on an active-substance-based review system and other potential alternatives for the environmental risk assessment (ERA) of veterinary medicinal products (VMPs).

It also outlines the conclusions of the Commission with regard to the potential impacts, as well as the practicability of possibly implementing a new approach to ERA at the current point in time, when the implementation of the new legal framework on VMPs has just begun and is still under development.

2. BACKGROUND

Both human healthcare and veterinary care rely on pharmaceuticals. About 3,000 active pharmaceutical ingredients (APIs) are authorised in either human or veterinary medicines, or in both, with a wide variability across Member States[2]. At present, some 600 APIs are authorised in VMPs in the EU. Some of the APIs are used also as active substances in biocidal products or plant protection products.

While the benefits of the responsible use of these substances in VMPs are widely recognised, there is concern over the potential adverse effects of these substances on the environment and on human health via the environment. The concern related to pharmaceuticals in the environment has been addressed by the legislators. The requirement for an ERA of VMPs as part of the marketing authorisation process was first introduced by Directive 92/18/EEC[3]. Applicants for new marketing authorisations (MAs) for VMPs are to provide an ERA, based on two successive phases[4]. In Phase I, the potential exposure of the environment to the VMP in light of the intended use is assessed. Phase II[5] is only to be performed for VMPs for which the Phase I concludes that, taking into account the exposure of the environment, there is a need for a more extensive assessment. This phase is structured around the risk quotient approach and combines the extent of exposure with further data on the fate and effects of VMPs on the environmental compartments of concern. Currently, ERA is based on several guidelines: Veterinary International Conference on Harmonization (VICH) Guidelines 6[6] and 38[7] and the Guideline[8] of the Committee for Medicinal Products for Veterinary

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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 (OJ L 4, 7.1.2019, p. 43)

2 European Commission, Directorate-General for Environment, Kümmerer, K., *Options for a strategic approach to pharmaceuticals in the environment: final report*, Publications Office, 2019, https://op.europa.eu/s/wEcR

3 Commission Directive 92/18/EEC of 20 March 1992 modifying the Annex to Council Directive 81/852/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (OJ L 97, 10.4.1992, p. 1)

4 *Ibid.*, Section 5.3 of the Annex.

5 *Ibid.*, Section 5.4 of the Annex.

6 Committee for Medicinal Products for Veterinary Use (CVMP), *Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products – Phase 1* (CVMP/VICH/592/98-FINAL), available at: https://europa.eu/!ytmMgd

Use (CVMP). Under Directive 2001/82/EC[9], all generic VMPs had to undergo an ERA regardless of whether such information was already available for the originator VMP. This requirement provided environmental information on a number of legacy products and helped improve environmental protection.

Similarly to the previous legislation[10], Regulation (EU) 2019/6 requires an ERA for new marketing authorisation (MA) applications according to the above-mentioned principles. However, with its entry into application on 28 January 2022, an ERA is no longer required for generic applications, except for generics for which the reference VMP was granted a MA before 1 October 2005[11]. Another important change is the possibility for the competent authorities (CAs), when harmonising summaries of product characteristics and in accordance with Article 72 of Regulation (EU) 2019/6, to request the marketing authorisation holder (MAH) to update the relevant environmental safety documentation of reference VMPs that were authorised before October 2005 and identified as potentially harmful to the environment[12].

The current product-based ERA system has a number of drawbacks: it does not guarantee a consistent and harmonised evaluation of the environmental risks of VMPs containing the same active substance; there is no legal obligation to review existing risk assessments to take into account scientific developments; there is a lack of transparency since the data are not publicly available; and VMPs authorised before October 2005 are not automatically revised by the competent authorities and thus do not have an ERA in line with the current guidelines.

In autumn 2020, the Commission appointed a contractor to conduct a feasibility study to identify, collect and analyse evidence of the appropriateness and practicability of moving towards an active-substance-based system instead of the current product-based one.

In its report[13], the contractor examined the possible impacts of an active-substance-based 'monograph system' along with two alternative proposals from the industry and assessed the efficiency and effectiveness of these proposals in achieving the objectives of Regulation (EU) 2019/6. For the conduct of the feasibility study, the contractor performed a literature search and exploratory interviews with stakeholders. Based on these, the contractor identified the sources of relevant evidence and remaining data

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7 Committee for Medicinal Products for Veterinary Use (CVMP), *Guidelines on Environmental Impact Assessment for Veterinary Medicinal Products Phase II* (CVMP/VICH/790/03-FINAL), available at https://europa.eu/!bRyWpH

8 Committee for Medicinal Products for Veterinary Use (CVMP), *Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38* (EMA/CVMP/ERA/418282/2005-Rev.1), available at: https://europa.eu/!fQjmTC

9 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1)

10 *Ibid.*

11 Regulation (EU) 2019/6, Article 18(7).

12 *Ibid.*, Article 72.

13 Schwonbeck, S., Breuer, F., Hahn, S., Brinkmann, C., Vosen, A., Radic, M., Vidaurre, R, Alt, J., Oelkers, K., Mezler, A., Floeter, C., *Feasibility Study of an Active-substance-based Review System ('Monographs') and Other Potential Alternatives for the Environmental Risk Assessment of Veterinary Medicinal Products*, EW-06-21-127-EN-N, European Union, Luxembourg, 2021, ISBN 978-92-76-42335-5, doi: 10.2875/94477, available at https://op.europa.eu/s/wvC9

gaps. In a second step the contractor attempted to fill in some of these data gaps by means of structured interviews and an online survey.

3. OVERVIEW OF THE MONOGRAPH SYSTEM AND THE ALTERNATIVES EVALUATED

Monograph system

The active-substance-based monograph system, proposed by Rönnefahrt *et al.*[14], provides for the set-up of an EU-wide uniform collection of relevant and high-quality environmental data for APIs used in VMPs on the EU market. The monographs would be mandatory for the APIs of VMPs that require an ERA with a Phase II assessment and antiparasitic VMPs for food-producing animals, as these are expected to lead to a greater exposure and negative impact on the environment.

The monograph system would contain information only on the APIs used in VMPs and not on specific VMPs. It would thus not constitute an approval system nor replace the ERA for a VMP, but rather deliver data to be used in the subsequent ecotoxicological evaluations at product level. The monograph for an API would thus contain the relevant environmental information, which is essential for the further development of the ERA for a VMP containing that API. In the current system each MAH needs to perform research to obtain these API data to prepare the ERA for the VMP. The monograph system would thus facilitate the development of product-based ERAs on the basis of the API data. Moreover, making the API environmental data publicly available would increase transparency and enhance the level-playing field for MAHs.

The minimum data in the monograph would be study summaries, endpoints of ecotoxicological studies, endpoints regarding physicochemical properties, and endpoints

[14] Rönnefahrt, I., *Experiences with environmental risk assessment in the authorization procedure of Veterinary Medicinal Products*, in *International Workshop on Eco-Pharmacovigilance of Veterinary Medicinal Products*. 2013, Federal Environment Agency, Dessau-Roßlau: 4.-5. December 2013, Berlin. p. 1-27, available at: https://www.umweltbundesamt.de/sites/default/files/medien/378/dokumente/roennefahrt_vortrag_veroeffentlichung_2.pdf , accessed on: 9 September 2022;
Rönnefahrt, I., *Monograph system of active pharmaceutical substances: necessity, challenges and perspectives*, in *Workshop „Monograph system on active pharmaceutical substances"*. 2014, Federal Environment Agency, Germany: Brussels, Belgium. p. 1-17, available at: https://www.ecologic.eu/sites/default/files/event/2015/4_monograph_system_workshop_2014_roennefahrt.pdf, accessed on: 9 September 2022
Rönnefahrt, I., N. Adler, and S. Hickmann. *Paradigm shift - Towards a substance-based environmental risk assessment of pharmaceuticals*. in *SETAC Europe Annual Meeting* 2016. Nantes, France: Federal Environment Agency, abstract available at: https://cdn.ymaws.com/www.setac.org/resource/resmgr/abstract_books/setac_europe_abstractbook_na.pdf, p. 305, accessed on: 9 September 2022
Rönnefahrt, I. and N. Adler, *Harmonised environmental information of pharmaceutical substances – the essential base for risk assessment and risk management* in *International Conference on Risk Assessment of Pharmaceuticals in the Environment (ICRAPHE)*. 2016, Federal Environment Agency: 8–9 September 2016, Paris, France. p. 1., abstract available at: https://www.acadpharm.org/dos_public/ICRAPHE_abstract_book_VF.pdf, p. 129, accessed on 9 September 2022
Rönnefahrt, I., *The ERA master file concept*, in *Workshop „How to achieve an appropriate Environmental Risk Assessment of Veterinary Medicinal Products"*. 2017, Federal Environment Agency, Germany: Brussels, Belgium, p. 1-14, available at: https://www.umweltbundesamt.de/sites/default/files/medien/362/dokumente/05_era_master_file_system_ronnefahrt.pdf, accessed on: 9 September 2022.

on environmental fate (degradation and adsorption), the highest Predicted Environmental Concentration in soil (PEC_{SOIL}) or the highest Environmental Introduction Concentration in water ($EIC_{aquatic}$) resulting from the existing Phase II ERAs for any VMPs containing the same API and authorised in the EU.

The monograph system would first focus on APIs authorised before October 2005 with priority on those of environmental relevance. It would be up to the Commission to develop a list of prioritised APIs.

For VMPs already authorised in the EU for which the environmental risk has been assessed in a Phase II ERA, the necessary data would be collected by all MAHs concerned. In the case of VMPs authorised prior to October 2005 for which an ERA is missing, all MAHs of VMPs with the same API would be legally obliged to collaborate in a consortium to deliver the environmental data required for the monograph.

In case of a new reference VMP containing a new API, the company applying for the MA would deliver the necessary environmental data according to the intended use of the substance in the new reference VMP. The scope of data in the monograph would depend on the use of the API in the VMP (e.g. a VMP for food-producing animals would in most cases require a Phase II ERA).

The draft monographs would then be assessed by EMA. All monographs would be stored in a database, e.g. hosted by EMA. Its content would be publicly available to all stakeholders, i.e. academia, environmental authorities, water managers, industry, etc.

However, the monograph system as proposed by Rönnefahrt *et al.* does not specify how the priority for existing substances would be set by the Commission, how data would be added if further VMPs with ERAs are authorised, the responsibilities of regulators and the industry, the procedural steps and timelines, costs compensations, which data would be included in the monograph and in what format, the approach to monograph updates, any potential fee structure, the database requirements and other practical aspects, leaving these aspects for a possible future legislative proposal amending or supplementing Regulation (EU) 2019/6. The contractor attempted to elucidate some of these aspects in their MONO4ERA proposal[15] which they assessed in parallel with the Rönnefahrt *et al*. proposal.

Proposal by AnimalhealthEurope

AnimalhealthEurope's (AhE) proposal is based on the legal obligation[16] for all EU CAs to publish a (European) Public Assessment Report ((E)PAR)[17] for each authorised VMP

[15] Schwonbeck, S., Breuer, F., Hahn, S., Brinkmann, C., Vosen, A., Radic, M., Vidaurre, R, Alt, J., Oelkers, K., Mezler, A., Floeter, C., *Feasibility Study of an Active-substance-based Review System ('Monographs') and Other Potential Alternatives for the Environmental Risk Assessment of Veterinary Medicinal Products*, p. 348, EW-06-21-127-EN-N, European Union, Luxembourg, 2021, ISBN 978-92-76-42335-5, doi: 10.2875/94477, available at https://op.europa.eu/s/wvC9

[16] Regulation (EU) 2019/6, Articles 44(10), 47(3), 49(11) and 52(11) read in combination with Article 55(2)(a)(v).

and is focused mainly on making the environmental data public. The existing (E)PARs would however need to be revised in order to include the results of environmental studies in a standard, harmonised format. The body responsible for the preparation of the revised (E)PAR would thus be the CAs in contrast to the monograph system proposal where most of the work would be done by the MAHs.

The system would cover new VMPs, already authorised VMPs with ERA but with no information in the (E)PAR, as well as VMPs authorised prior to 2005 and without ERA in the following way:

- For already authorised VMPs, the CAs should use the substantial datasets already available to them to revise the existing (E)PARs to include the available environmental study results for products with a Phase II ERA, where this is not already the case.

For VMPs authorised prior to October 2005 and lacking an ERA, the proposal is limited to the cases where a summary of product characteristics (SPC) harmonisation is initiated. A product can be proposed for SPC harmonisation by the CAs or by the MAH. However, it is up to the coordination group (CMDv[18]) to establish the priorities for this SPC harmonisation. For the update/drafting of environmental information in the (E)PAR, the CAs are to take into account all information available from both reference and generic VMPs and if necessary, request the MAHs to provide the required information to update the (E)PAR based on Article 72 of Regulation (EU) 2019/6.

The (E)PAR would contain information on the VMP itself, environmental data on the API and a summary of the ERA in a standard, harmonised format. The AhE proposal contains a tentative data table that could serve as a basis for the development of a harmonised format. But cooperation between CAs, and possibly the industry, would be needed to agree upon a standard, harmonised format. The (E)PARs would be centralised in the Union Product Database (UPD) referred to in Article 55 of Regulation (EU) 2019/6 and made available to the public in accordance with Article 56(3) of that Regulation.

In the AhE proposal, the ERA remains linked to the VMP and its patterns of use, whereas the monograph system is limited to the hazards posed by the API.

However, the AhE proposal lacks clarity on the timeline for the revision of the existing (E)PARs; how this could be imposed on the CAs; how a harmonised approach ensuring coherent, consistent and complete environmental information in all (E)PARs could be established and how the work would be prioritised. In the absence of a legally enforceable timeline, the completeness of the system would depend on the willingness and ability of the individual CAs to provide the necessary resources for the revision of a

[17] The public assessment report in the case of marketing authorisation procedures other than the centralised one and the European public assessment report in the case of the centralised procedure is a document or set of documents describing the scientific evaluation and reflecting the conclusion reached by the regulators at the end of the evaluation process. It provides a summary of the grounds for approval (or refusal) of the marketing authorisation for the specific veterinary medicinal product. It is made available to the public, after the deletion of commercially confidential information.

[18] Coordination group for mutual recognition and decentralised procedures veterinary medicinal products established under Article 142(1) of Regulation (EU) 2019/6.

high number of (E)PARs. Without a clear legal framework, implementation of the AhE proposal would also depend on the CAs agreeing to the revision of guidelines on the (E)PAR to have a harmonised data presentation.

Proposal by Access VetMed

Access VetMed (previously named European Group for Generic Veterinary Products – EGGVP) also proposed an alternative system. Its scope is limited to reference and generic VMPs authorised before October 2005. The proposal considers that VMPs authorised after October 2005 have sufficient ERA data available. For reference VMPs authorised before October 2005, the CA would conduct a risk-based review of the respective VMP in order to categorise its environmental risk, e.g. as 'high', 'medium', 'low', or 'very low', based on the data and 'know-how' currently available.

This categorisation system would trigger the need and indicate the priority to perform an ERA scientific review consisting of the following steps: identification of all existing MAs using the UPD, collecting all available ecotoxicological data, complementing with data from other sources, conducting a scientific review of the data and proposing and publishing a final set of endpoints and other specific ERA data.

In the event of a reference VMP authorised before October 2005, identified as potentially harmful to the environment and with no corresponding generic VMP authorised after October 2005 (which would thus have the necessary ERA data), the MAH would be responsible for the generation or update of the ERA data.

Like in the AhE proposal, the body responsible for the above steps would be the CA, but MAHs would provide ERA data, if required.

The main difference with the AhE proposal is that in this proposal CAs would not be required to revise the (E)PARs for VMPs authorised after October 2005 and the ERA data of these products might thus not be publicly available.

Like the AhE proposal, the Access VetMed proposal lacks clarity on the timeline for the risk-based review of the VMPs authorised before October 2005; how this could be imposed on the CAs; how a harmonised approach ensuring coherent, consistent and complete environmental information in all (E)PARs could be established and how to ensure that there would be no difference in approach among CAs to the environmental risk categorisation of the APIs.

4. ANALYSIS OF THE ADVANTAGES AND DISADVANTAGES OF THE MONOGRAPH SYSTEM AND THE ALTERNATIVE PROPOSALS

4.1. Advantages

Higher quality of ERA data

Due to the review and compilation of the ERA data, the data in the monograph system would be more robust and of higher quality. For some VMPs authorised before October 2005, new ERA data would need to be generated according to current guidelines. By

pooling resources, the efficiency in the generation of such new data would be improved, e.g. when conducting cost-intensive studies with radiolabelled APIs.

In comparison, the two alternative proposals, being based on product specific data and not on substance-based data, would not solve issues such as inconsistent assessments, limited availability of environmental information and would thus have a limited contribution to the improvement of the quality of ERA data.

Enhanced access to ERA data

With the current system, environmental authorities and experts such as researchers do not have sufficient access to ERA data. With a monograph system and its implementation in a database, the requirements of the Aarhus Convention[19] regarding public access to environmental information and increased transparency for all stakeholder groups would be met.

The two alternative proposals remain focussed on product evaluation. Therefore, they would not solve the current issue of identifying harmful active substances and the access to ERA data would remain limited since these data would need to be searched in the EPARs of individual VMPs. Moreover, the Access VetMed proposal is limited to reference VMPs authorised before October 2005 and would thus result in a less complete database than the two other proposals.

Enhancement of the level playing field for MAHs

Equal treatment of ERA and Risk Mitigation Measures (RMM) across all MAHs of products containing the same API and using the same route of administration would be improved with the monograph system. Moreover, an active-substance-based system would be a prerequisite for the same substances to be assessed consistently ensuring higher environmental protection.

The two alternative proposals are centred on product evaluations and would therefore not contribute to the enhancement of a level playing field as each MAH would need to generate its own data and this could lead to different conclusions for individual products with the same API.

Guaranteeing the highest level of protection of public and animal health and of the environment

The monograph system would encompass valuable information regarding AMR such as effects on the microbial community, effects on cyanobacteria, physicochemical properties and estimates of the concentrations of the substance released to the environmental compartments. This would support the One Health approach.

The monograph system would also include the assessment of whether substances are persistent, bioaccumulative and toxic (PBT) and thus increase the availability of data

[19] Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters, United Nations, Treaty Series, vol. 2161, p. 447, https://unece.org/DAM/env/pp/documents/cep43e.pdf

important for assessing biomagnification in the food-chain and further residue analyses to protect human and animal health.

Furthermore, the monograph system would contribute to the development of RMMs to reduce the pollution of surface water, groundwater and drinking water supply.

By avoiding test duplication, the monograph system would also reduce the number of test animals used, e.g. in ecotoxicology testing.

The two alternative proposals, remaining centred on individual product evaluations, would provide limited benefits as they would not harmonise the environmental data in the ERAs of different products. They would only harmonise the way in which the environmental data are presented in these ERAs.

4.2. Disadvantages

Administrative burden and cost for CAs

After an initial phase of system setup, the monograph system is expected to reduce administrative burden by minimising redundancies in the process of generating and providing product-based ERA for the same API.

Compared to the current system, the monograph system would involve additional costs and administrative tasks for the CAs, the veterinary pharmaceutical industry, the Commission and EMA. According to the estimations made by the contractor, the administrative burden for CAs for establishing and approving a monograph would approximate to EUR 4,355/application, and the monetised burden for the CAs for assessing the ERA on an existing monograph is estimated to be EUR 2,497/application. A full process in the monograph system would thus total approximately EUR 6,852 (EUR 4,355 for establishing the monograph + EUR 2,497 for assessing the ERA for a VMP), adding an additional cost of approximately EUR 3,027 for the assessment of the initial ERA for an API against the approximately EUR 3,825 under the current system. Since the cost for establishing the monograph is a one-off, the cost for subsequent ERAs for VMPs containing the same API would be lower than in the current system. Starting with the fourth marketing authorisation process involving the same API, the administrative burden of the monograph system would be lower than in the current system. However, given that according to Article 18 of Regulation (EU) 2019/6 generic applications no longer require an ERA (except in exceptional circumstances), it is unlikely that this situation of four ERAs for the same API would ever occur.

It should be noted that a monograph system would cause a partial shift of the administrative burden from the national to the EU level (EMA), because the monograph system and associated study assessment are to be centralised at EU level.

The total costs of the monograph database in the first year were estimated to be around EUR 66,800 for an external database (developed, maintained and stored by a third party), and EUR 67,200 for an internal one (developed, maintained and stored by EMA). Annual costs in the following years have been estimated to amount approximately to EUR 7,200 and EUR 5,900 for an external and internal database, respectively.

It should be noted however that the feasibility study report warns that there is a number of uncertainties and assumptions associated with the cost-estimation. The limited information available did not allow a precise assessment, nor an estimate of the overall impacts in order to objectively determine the associated costs. In interviews with the contractor and in the online survey, CAs expressed their difficulties in estimating the person hours needed for a not yet established system. The cost calculation thus seems very low and does not take into account the cost for reviewing the existing risk assessments in view of scientific progress. The study recommended gathering more facts and figures in order to close the remaining knowledge gaps.

Moreover, the cost-estimation was criticised by AhE and AccessVetMet. According to the industry, the costs are largely under-estimated and based on inaccurate and unrealistic assumptions.

No cost estimation was made by the contractor for the two alternative proposals. Therefore, no complete cost comparison can be made between the three proposals making it impossible to conclude on their individual impacts. However, taking into account that both alternative proposals put more responsibility upon the CAs for the preparation of the revised (E)PARs, these proposals will be more cost- and resource-intensive for the CAs, while triggering lower costs for industry.

As the monograph system is expected to increase the burden on the industry (especially on the innovative industry) while the two other systems are expected to increase the burden on the CAs, all three proposals conflict with the objective of the Regulation (EU) 2019/6 to reduce administrative burden.

Impact on availability and functioning of the internal market

The industry (14 out of 15 respondents, overwhelmingly from the generic industry) and some CAs (3 out of 15 respondents) expect a monograph system to have a negative impact on the availability of VMPs. This could be especially relevant for niche markets or in smaller EU Member States with already small numbers of VMPs authorised. Products without ERA data could be withdrawn from the market should the costs of monograph establishment occur. In fact, some of the active substances which currently do not have an ERA are included in VMPs intended for limited markets, generating low profits for MAHs (e.g. VMPs for minor species such as rabbits, bees, aquaculture species and goats or for infrequent diseases). An option to mitigate this issue could be to provide for the possibility of exemptions from the monograph requirement for MAHs of products for limited markets. However, this would likely have an impact on the completeness of the system and increase costs for the MAHs of the other products. Moreover, this would not solve the issue for MAs in smaller MS, where VMPs might be withdrawn if the applicant is forced to contribute to a consortium for establishing a monograph.

For innovator companies, the monograph system would likely generate additional costs due to the fees for assessment and maintenance of the monographs, administrative burden, consortium costs and data management costs. This would lead to a further decrease in attractiveness of the EU region regarding market entry for products with new APIs, amplifying the trend towards fewer authorisations of VMPs based on new APIs.

Since the alternative proposals (AhE and Access VetMed) require less additional costs and administrative burden for MAHs than the monograph system, but rather additional costs and burden for the CAs, both are expected to have less impact on the availability of VMPs than the monograph system. In light of the additional burden for the CAs, the alternative proposals might however create delays in the assessment at the level of the CAs or the need for CAs to increase their fees.

Uncertainty on fees and data access/protection

Clear and proportionate rules for access to monographs would need to be legally defined to ensure that the market is not distorted. Respondents expressed their concerns that if only a few major players controlled fees for access to data as part of the collaborative effort required by the monograph system, the costs could become unsustainable for SMEs.

In general, there were concerns about how SMEs would adapt to the monograph system and if they would be able to benefit from collaborative efforts. Limited protection of intellectual property rights due to requirements for cooperation was also mentioned as a disadvantage.

The two alternative proposals do not have the same drawbacks with regards to rules for access and potential fees linked to this access.

5. ADDITIONAL CONSIDERATIONS

Impact on the veterinary vs. the human pharmaceutical industry

The production and use of human medicinal products also have an impact on the environment. Taking into account the relative size of the VMP market (only about 3% of the market size for human medicinal products), the additional effort that the monograph system would place on the veterinary pharmaceutical industry could be considered as excessive compared to the human pharmaceutical industry and may not alone be sufficient to ensure a higher level of environmental protection.

As explained above, the two alternative proposals are expected to place less administrative burden upon the pharmaceutical industry than the monograph system. However, these proposals would be expected to put additional costs and burdens on the CAs for VMPs, which could lead to an increase in the fees imposed by these CAs. This could create a further burden that would not be applicable in relation to human medicinal products.

Acceptance

CAs from eight Member States have expressed their support for the development of a centralised API monograph system. No other stakeholders expressed positions.

Industry has already invested in establishing ERAs for most generics and originator products and is strongly concerned about reassessment and the additional costs that a monograph system would bring. As mentioned before, industry considers that the costs and resources needed for a monograph system are largely under-estimated in the

feasibility study and the respective report does not consider nor address the practical hurdles linked to the implementation of a monograph system.

Revision of the legal framework

Introducing the monograph system would necessitate amendments of Regulation (EU) 2019/6 as outlined in the MONO4ERA proposal. This would include, for instance, introducing requirements for applicants to provide a draft monograph as part of the technical documentation referred to in Article 8(1)(b) in conjunction with Annex II; for MAHs of existing VMPs to jointly generate, use and submit environmental information to the CAs; for sharing the monographs among MAHs; for the Commission to adopt a programme for the gradual establishment of monographs for APIs already on the market (catch-up procedure) and prioritisation of APIs; for regular updates of the monographs as part of the obligations of MAHs under Article 58; for data protection; for the monograph database; as well as for sanctions under Article 130(3) for failure to fulfil the obligations regarding the establishment of monographs.

In theory, both alternative systems (AhE and Access VetMed) could be put in place without a revision of the current legal framework. However, in practice, the success of both systems would depend entirely on the willingness of the CAs to conduct the necessary work. In the absence of a clear legal framework imposing a timeline, a common approach and prioritisation of the effort by the CAs, both proposals are likely not to work.

All three systems proposed would thus require a revision of the current legal framework for VMPs.

6. CONCLUSIONS

The active-substance-based monograph system and the two alternatives that have been evaluated could to varying degrees contribute to improving environmental protection.

The monograph system would best optimise, improve and consolidate hazard data on active substances for ERA, improve knowledge about relevant environmental risks, avoid duplication of tests on vertebrate animals and thus contribute to the 3 R's (Replace, Reduce, Refine), lead to a higher quality of ERA data, allow environmental information to be gained more efficiently and give environmental authorities, experts and the public access to ERA data. In the long term, the administrative burden on the authorities and industry is expected to be reduced. However, this effect of reducing the administrative burden is not guaranteed[20].

The monograph system would enhance the protection of the environment thus supporting one of the main objectives of Regulation (EU) 2019/621. Moreover, the monograph system could ensure a consistent assessment of VMPs containing the same active substances.

[20] See section 4.2 – Administrative burden and cost for CAs.

[21] See section 4.1 – Guaranteeing the highest level of protection of public and animal health and of the environment

The two alternative proposals remain centred on product evaluation. Therefore, they would not address some of the drawbacks of the current system, such as inconsistent assessments, limited availability of environmental information, and the remaining difficulty to identify harmful active substances. These alternatives would not result in significant improvements regarding protection of the environment and of animal and human health. Moreover, both proposals lack clarity on the timeline, the legal enforceability, how a harmonised approach between the CAs can be ensured and how the work should be prioritised.

Therefore, only the monograph system would contribute to meeting the general objectives of Regulation (EU) 2019/6 (except for the envisaged reduction of administrative burden, at least initially) and support the EU Strategic Approach to Pharmaceuticals in the Environment[22] and the 'one substance, one assessment' approach as specified in the Green Deal[23] and the Chemicals Strategy for Sustainability[24].

The monograph system represents a significant shift in the VMP authorisation process. The changes needed for the implementation of a monograph system (including of legislative nature), would be a major challenge for the veterinary regulatory network (CAs, EMA and the Commission) and the industry.

During the implementation phase, the monograph system and the two proposed alternatives would give rise to additional costs for already authorised VMPs and are likely to be more cost- and resource-intensive than the current system of a complete ERA evaluation for each individual VMP application. The costs for applicants of new MAs of VMPs could be higher under the monograph system in comparison with the current system and the two alternatives proposed. Consequently, a negative impact on availability of VMP cannot be excluded and cost pressure on SMEs could increase.

The implementation of Regulation (EU) 2019/6 is still developing. It calls for the adoption of some 25 delegated and implementing acts, about half of which needed to be adopted before or by the date of application, 28 January 2022. The next package of acts the Commission will focus on are mostly due by 2025, with one act due by 2027. Apart from the legislative work, since the adoption of the Regulation in 2018, the resources and effort of the CAs and the industry have been directed at implementing the new legal framework on the ground. This has been and continues to be very demanding and burdensome for the network and the industry. Moreover, the effects of the current system in relation to ERA, such as the impact of Article 18(7) on generic applications and Article 72 on legacy products that have not been subject to an ERA, will need time to materialise. Therefore, introducing the monograph system or any of the two proposed alternatives, in addition to the measures and approaches that would need to be put in place in order to implement Regulation (EU) 2019/6, would seem to be premature at

[22] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE European Union Strategic Approach to Pharmaceuticals in the Environment (COM/2019/128 final)

[23] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE EUROPEAN COUNCIL, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS The European Green Deal (COM/2019/640 final)

[24] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. COM(2020) 667 final

this point in time and would impose excessive demands on already overstretched resources.

The implementation of a monograph system could be reconsidered once Regulation (EU) 2019/6 is completely implemented and its impacts in practice (i.e., availability of VMPs, administrative burden, impact of SPC harmonisation etc.) become clearer. This would then also require more certainty on the costs linked to the implementation of such an active-substance-based system and its further impacts on the availability of VMPs.

In order to have a comprehensive and coherent system, the monograph system must be considered in a broader context, beyond the VMP sector. In light of the overall number of APIs in medicinal products on the EU market25, a system collecting the environmental data of those used in VMPs would only cover a small portion of the APIs on the market and result in an incomplete database.

The ongoing work on a future Commission proposal to revise the general legal framework for human medicinal products would likely include new ERA requirements. Therefore, it is appropriate to wait for the outcome of this process before considering implementing the monograph system for VMPs.

In the meantime, the Commission will explore, in close cooperation with the CAs, the possibilities to improve and harmonise the current system as much as possible. Measures could be agreed upon to facilitate the potential future implementation of a monograph system, without impacting the workload of the CAs nor requiring any change to the existing legal framework.

[25] See Background section.

LIST OF ABREVIATIONS

AhE	AnimalhealthEurope
AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
CA	Competent Authority
$EIC_{aquatic}$	Environmental Introduction Concentration in water
EMA	European Medicines Agency
(E)PAR	(European) Public Assessment Report
ERA	Environmental Risk Assessment
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PEC_{SOIL}	Predicted Environmental Concentration in soil
PBT	Persistent, Bioaccumulative, and Toxic
RMM	Risk Mitigation Measures
SPC	Summary of Product Characteristics
UPD	Union Product Database
VICH	Veterinary International Conference on Harmonisation
VMP	Veterinary Medicinal Product