Integrated Environmental Assessment and Management — Volume 00, Number 00—pp. 1–12
Received: 14 October 2020 | Returned for Revision: 21 December 2020 | Accepted: 15 April 2021

Environmental Policy & Regulation

European legislation for veterinary medicines: Would a monograph system improve the environmental risk assessment?

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Abstract

The environmental risk assessment (ERA) of veterinary medicinal products (VMPs) has been a regulatory requirement in the European Union (EU) since 1993. However, in the last few years, the potential impact of human and veterinary medicines on the environment has become a growing concern worldwide. Indeed, the legal requirements for VMPs in the EU are changing. Regulation (EU) 2019/6, which will be applied from January 28, 2022, aims to update the regulatory framework for VMPs and replaces Directive 2001/82/EC. This paper analyzes the ability of both legislations to ensure a high level of protection of the environment while authorizing VMPs. Consideration is also given to the impact on administrative burdens in both the legislations. We conclude that the Regulation improves the Directive by reducing to a certain extent the regulatory burdens for the applicants and authorities. However, the knowledge of the environmental risks of all authorized VMPs and the consistency of the assessments remain quite similar between both legislations. Nevertheless, the new Regulation proposes to examine the feasibility and applicability of an assessment system based on the critical review of properties of the active substances ("monographs") or other potential alternatives. With this in mind, two proposals (a basic and an enhanced approach) for developing a monograph system are presented and their main advantages and disadvantages are explored. *Integr Environ Assess Manag* 2021;00:1–12. © 2021 The Authors. *Integrated Environmental Assessment and Management* published by Wiley Periodicals LLC on behalf of Society of Environmental Toxicology & Chemistry (SETAC)

KEYWORDS: Directive 2001/82/EC, Environmental risk assessment, Monograph, Regulation (EU) 2019/6, Veterinary medicinal product

INTRODUCTION

The potential impact of human and veterinary medicines on the environment is a growing concern around the world. It has led to the launch of significant international initiatives in recent years to tackle the issue. For instance, in 2015, a strategic approach to international chemical management (SAICM) was initiated. It is a policy framework of the United Nations Environment Programme (UNEP) that specifically recognized "environmentally persistent pharmaceutical pollutants" as an issue to be urgently addressed (SAICM/ICCM.4/7, 2015). Furthermore, in 2019, the Organisation for Economic Co-operation and Development (OECD) acknowledged the risks to the environment emanating from released residues of medicinal products in the "pharmaceuticals in fresh water" report. It recommends, inter alia, to establish a centralized database to share the ERAs and to prevent duplication of efforts (OECD, 2019). In the same year, the European Commission (EC) also acknowledged the presence and effects of pharmaceuticals on the environment in its "European Union strategic approach to pharmaceuticals in the environment" (EC, 2019b). It proposed actions such as "catching-up" procedures for older VMPs for which an adequate ERA has not been performed (so-called "legacy products"). Furthermore, the European Green Deal was presented in December 2019 by the newly instated EC, and one of its policy areas aims to reduce pollution and to improve the conditions on the assessment of (chemical) substances before their launch in the internal market (EC, 2019a). In line with the objectives of the Green Deal, the EC "farm to fork strategy" aims to ensure sustainable food production by reducing, among others, the use of antimicrobials in food-production animals and aquaculture (EC, 2020a).

Legislation in the EU is starting to address the issues and actions proposed in the initiatives mentioned above. For

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Published 20 April 2021 on wileyonlinelibrary.com/journal/ieam.

TABLE 1 Development of ERA guidelines for VMPs over the years

Date of coming into effect	Guideline	ERA requirements/criteria
April 1, 1993	Directive 92/18/EEC	General requirement to perform an ERA for new MA divided into two phases (Phases I and II)
January 1, 1998	EMEA/CVMP/055/96-FINAL	First guidance on how to conduct Phase I and Phase II ERA. No details on exposure calculation were provided
July 20, 2000	VICH GL6	Harmonized guideline on how to conduct Phase I ERA based on a decision tree; no details on exposure calculation were provided
October 1, 2005	VICH GL38	Harmonize guideline on how to conduct Phase II ERA; details on the environmental fate and toxicity data required to perform the Phase II assessment were included; no details on exposure calculation were provided
November 1, 2007	EMA/CVMP/ERA/418282/2005	Guideline in support of VICH GL6 and 38, where further explanations were provided for some points; details on how to calculate the exposure were included

Abbreviations: ERA, environmental risk assessment; MA, marketing authorization; VMP, veterinary medicinal product.

example, since 2015, a "watch list" aimed at identifying emerging pollutants in surface waters has been published. In recent years, it has been populated with different pharmaceutical substances through Directive 2008/105/EC as amended ("environmental quality standards in the field of water policy directive"). This Watch List included different pharmaceutical substances in its first publication and later updates, that is, amoxicillin, ciprofloxacin, trimethoprim, sulfamethoxazole, venlafaxine, and its metabolite *O*-desmethylvenlafaxine, clotrimazole, fluconazole, and miconazole (EC, 2018, 2020b). Moreover, Directive 91/271/EC ("urban waste-water treatment directive") was reviewed at the end of 2019, which led to the conclusion that ways to deal with contaminants of emerging concern reaching water bodies, for example, pharmaceuticals, need to be established. Lastly, Regulation (EU) 2019/6 ("new veterinary regulation" [NVR]), which will be applicable from 2022, considers this increased interest in environmental protection and enacts certain measures accordingly. For instance, among the measures implemented, the NVR requests the EC to investigate the feasibility of an active substance-based review system (the so-called "monograph system") and other potential alternatives suitable for the ERA of VMP in the EU. A substance-based assessment is already used in other regulatory frameworks before the product authorization. For instance, Regulation (CE) 1107/2009 concerning the placement of plant protection products (PPP) in the market establishes that an application for the approval of an active substance shall be submitted by the producer of the active substance to a Member State (MS), together with a summary and a complete dossier containing all the information required in Regulations (CE) 283/2013 (concerning the active substance) and (CE) 284/2013 (concerning the formulated product). The MSs (under a [co]rapporteurship system), the European Food Safety Authority (EFSA), and the Commission evaluate every active substance for safety before it can be placed in the market and used in a PPP. Before a substance can be approved, it must be proved to be safe for people's and animal's health and the environment. Similarly, Regulation (EU) 528/2012 concerning biocidal products also requires the approval of the active substance at the European level before the use on any product. It implies the submission of a complete dossier and the assessment by an MS competent authority (CA). The results of these evaluations are forwarded to ECHA's Biocidal Products Committee, which prepares an opinion. The opinion serves as the basis for the decision on approval that is adopted by the European Commission.

The basic principle of ensuring a high level of protection of the environment in the frame of the authorization of VMPs has been present in EU legislation since the early 1990s. In 1993, Directive 92/18/EEC came into force and requested applicants for new marketing authorizations (MAs) to provide an ERA based on two successive phases or tiers. In Phase I, the potential environmental exposure of the VMP in question is calculated. If a certain exposure limit was surpassed, then an assessment of the VMP ecotoxicity should proceed. However, formal guidance on how to perform an ERA was not developed until 1998 (EMEA, 1998), a date that can be generally regarded as the starting point of the current basic ERA principles established for VMPs. Some years later, these principles were further developed, which culminated in the publication of VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products) guidelines (GL) 6 ("Guideline on environmental impact assessment [EIAs] for veterinary medicinal products—Phase I" [CVMP/VICH/592/98-FINAL]) and 38 ("Guideline on environmental impact assessment for veterinary medicinal products—Phase II" [CVMP/VICH/790/03-FINAL]) (European Medicines Agency [EMA], 2000, 2004). These two guidance documents are still in force and represent a basic milestone in the harmonization of the performance of an ERA. They set out the decision tree to follow in Phase I (EMA, 2000) and in the standardization of data required for performing an ERA in Phase II (EMA, 2004). However, none of these guidance documents define how to

TABLE 2 ERA reflection papers and guidelines currently in force for VMPs

Date of coming into effect	Guideline
July 20, 2000	VICH GL6 Guideline on environmental impact assessment (EIAs) for veterinary medicinal products—Phase I
October 1, 2005	VICH GL38 Guideline on environmental impact assessment for veterinary medicinal products—Phase II
First adopted: November 1, 2007 Second revision adopted: March 1, 2009	EMA/CVMP/ERA/418282/2005-Rev.1- Corr.1 Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38
March 11, 2011	EMA/CVMP/ERA/430327/2009 Guideline on determining the fate of veterinary medicinal products in manure
March 8, 2012	EMA/CVMP/ERAWP/409328/2010 Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products
April 1, 2016	EMA/CVMP/ERA/52740/2012 Guideline on the assessment of persistent, bioaccumulative, and toxic (PBT), or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products
October 1, 2017	EMA/CVMP/ERA/689041/2015 Guideline on the plant testing strategy for veterinary medicinal products
November 1, 2018	EMA/CVMP/ERA/103555/2015 Guideline on assessing the environmental and human health risks of veterinary medicinal products in groundwater

Abbreviations: ERA, environmental risk assessment; VMP, veterinary medicinal product.

exactly calculate the potential exposure of different environmental compartments to VMPs. This is a basic need for determining the environmental risks associated with the use of a product. This was rectified in a later guideline (EMA, 2016), which came into effect in 2007 (and was amended in 2009). It provided equations and models to predict the exposure of VMPs in various environmental compartments (Table 1).

The current legal requirements have been in force since 2005, when Directive 2004/28/EC amending Directive 2001/82/EC came into force. Since then, an ERA has not only been required for new products according to article 12(3) of Directive 2001/82/EC, but also for new applications for all types of products, such as generics. This new requirement was not systematically implemented until 2009, when the European Commission published a Notice to Applicants with detailed guidance on the procedures that require an ERA (NtA 6C, 2009). The year 2009 can be regarded as the date from which the current system for ERAs began by considering the foundations laid by the EMA guidance on how to perform the assessment and the Notice to Applicant guidance with clear indications on which procedures need an ERA. Since then, further reflection papers, question and answer documents, and guidelines have been published by EMA. They cover specific needs during the authorization process that, due to the scientific progress, were not enough developed in the abovementioned guidelines (Table 2).

As can be seen, the evolution in the ERA guidelines over the years has unfortunately led to VMPs being available in the EU market with different requirements and approaches regarding environmental risk assessment; for example, VMPs authorized before 1998, for which not even a basic ERA was carried out, share a market with VMPs authorized using an out-of-date ERA approach (i.e., those products authorized between 1998 and 2009) and VMPs being authorized using current guidances (i.e., products authorized after 2009; Table 1).

Considering the importance of ensuring a high level of environmental protection, the present document aims to reflect on the performance of the current and upcoming EU VMP legislation (i.e., Directive 2001/82/EC and Regulation (EU) 2019/6) in fulfilling this basic principle. In addition, the impact of the legislation burdens will be examined. The possibility of the development of an active substance-based review system to improve the assessment of VMPs is explored and its main advantages and disadvantages are briefly described.

EUROPEAN LEGISLATION AND PROCEDURES FOR THE ERA OF VMPs

Procedures and types of applications for an MA and principles of the ERA

In the EU, no VMP can be placed in the market without being granted an MA by the European Commission (only applicable to centrally authorized VMPs; see Table 3) or a national competent authority (NCA). There are four different procedures to obtain an MA in the EU (Table 3): national, decentralized, mutual recognition, and centralized procedures. In accordance with the relevant legislation, each of them has its own processes and timelines (Directive 2001/82/EC; Regulation (EC) 726/2004; Regulation (EU) 2019/6).

 DOI: 10.1002/ieam.4431

TABLE 3 Summary of the different type of procedures available for the authorization of VMPs in the EU

Type of procedure	Characteristics
National	Assessed and approved on a national basis only. The marketing authorization is granted only in the concerned MS
Decentralized	Assessed and approved by NCAs of several MSs. The marketing authorization is granted in all concerned MSs
Mutual recognition	Applicable only to nationally authorized VMPs pursuing authorization in additional MSs. The MA is granted in all concerned MSs
Centralized	Assessed by the EMA and approved by EC at the European level involving all MSs. The MA is granted for the whole EU. This type of procedure is compulsory for some types of products (e.g., innovative products) and optional for others

Abbreviations: EC, European Commission; EMA, European Medicines Agency; ERA, environmental risk assessment; EU, European Union; MS, Member State; NCA, national competent authority; VMP, veterinary medicinal product.

Regardless of the procedure followed for the MA, the dossier provided in support of the application has to contain all the information detailed in the relevant legislation to ascertain its quality, safety, and efficacy. There are derogations to this general rule that allow applicants to waive certain requirements. Applications that provide all the documentation requested by the legislation are commonly referred to as "full applications." Applications waiving certain parts of a dossier are termed differently depending on the extent of the requirement reduction (e.g., generic, hybrid, or informed consent applications; Table 4).

To obtain an MA, the applicant needs to comply with the scientific criteria required by legislation in relation to the quality, safety, and efficacy of the VMP. The safety part includes environmental safety where the applicant has to assess the impact on the environment that the VMP in question might have. This should follow a two-tiered approach in accordance with VICH GLs 6 and 38 (EMA, 2000, 2004). The first phase (Phase I; detailed in VICH GL6) yields an estimate of exposure of the VMP in question to the primary receiving compartments, that is, soil or water. If a certain exposure limit is surpassed or if the VMP is a parasiticide used in pasture animals, a Phase II assessment according to VICH GL38 should be performed. In the "Phase II assessment," a risk quotient (RQ) for each affected environmental compartment is calculated by dividing the predicted environmental concentration by the predicted no-effect concentrations obtained from ecotoxicity studies using relevant endpoints. The RQ obtained is then compared with a threshold value of 1, with the risks being unacceptable if the RQ is equal or higher than 1 and acceptable if it is under 1. A Phase II ERA can be further divided into three increasingly complex tiers (tier IIA, tier IIB, and tier IIC). These are sequentially applied depending on whether the RQ is below (i.e., no risk) or above (i.e., risk) the value of 1 in a lower tier. In tier IIA ERA, which can be considered the "basic" phase II ERA, simpler ecotoxicological studies and endpoints are required to produce a conservative assessment of risk. If such data reveal that the exposure of an environmental compartment to the VMP in question constitutes a risk for the environment (i.e., RQ > 1), the applicant is required to progress to testing according to more complex approaches in tiers IIB and IIC to refine the ERA (EMA, 2004).

Directive 2001/82/EC versus Regulation (EU) 2019/6: Main differences regarding ERA requirements

The NVR, which repeals Directive 2001/82/EC, does not change the technical ERA methodology described above. Nevertheless, there are significant procedural changes

TABLE 4 Legal basis for data requirements of each MA procedure for veterinary pharmaceuticals according to current and future legislation (Directive 2001/82/EC and Regulation (EU) 2019/6)

Type of application/procedure	Directive 2001/82/EC as amended (applicable until January 28, 2022)	Regulation (EU) 2019/6 (applicable from January 28, 2022)
Full[a]	Article 12(3)	Article 8
Generic[b]	Article 13(1)	Article 18
Hybrid[b]	Article 13(3)	Article 19
Well-established use/bibliographic data[b]	Article 13a	Article 22
Fixed combination VMPs[b]	Article 13b	Article 20
Informed consent[b]	Article 13c	Article 21

Abbreviations: MA, marketing authorization; VMP, veterinary medicinal product.
[a]Applications that provide all the documentation requested by the legislation.
[b]Applications waiving certain parts of a dossier are termed differently depending on the extent of the requirement reduction.

between the two legislations that deserve attention. Comparing the two legislations, we have found that the main changes have taken place in the following areas: type of applications requiring an ERA (article 18.7), catch-up procedures for older products (article 72), authorization of VMPs containing (very) persistent, (very) bioaccumulative, and toxic (PBT and vPvB) substances (article 37.2), use of VMPs in aquaculture outside the terms of authorization (article 114.3), and substance-based assessment (article 156).

Considering the aims of this paper, we will compare below the different approaches of the Directive and the NVR in relation to the types of applications requiring an ERA, the catch-up procedures, and the substance-based assessment.

Directive 2001/82/EC

- An ERA according to VICH and EMA guidelines should be requested for all types of MA applications, irrespective of the type or procedure of authorization (see Tables 3 and 4) or if the active substance had already been reviewed in the frame of previous MA procedures.
- The Directive does not include provisions for a "catching-up" procedure for older products (so-called "legacy products") that are still in the market but for which an ERA was not performed at the time of the authorization (i.e., products authorized before 1997; see Table 1 for details).
- In relation to the substance-based assessment, the ERA carried out under the Directive is product-based. This means that the risks for the environment of a certain substance are repeatedly assessed during the authorization of each VMP that contains such substance.

Regulation (EU) 2019/6 (NVR)

- An ERA should be performed for full applications and for generic products whose reference product was authorized before October 1, 2005. Setting the threshold date for the requirement of an ERA to October 1, 2005 is probably directly related to the date when the VICH GL38 came into effect. Therefore, it would be assumed that an ERA according to that guideline would have been performed for all the VMPs authorized after that date.
- The NVR does not specifically foresee a "catching-up" procedure for "legacy products" (i.e., products authorized before 1997; Table 1). However, the summary of product characteristics harmonization ("SPC harmonisation") procedure laid down in articles 70–72 of the NVR allows the review of nationally authorized reference products and their generics. Article 72 states that in the frame of the "SPC harmonisation" procedure, an ERA may be required for those reference products that were authorized before October 1, 2005. The application of these articles might imply the revision of some "legacy products." Nonetheless, it should be noted that this procedure does not entail a general systematic review of VMPs regarding their ERA status, and thus will not necessarily cover all legacy products concerned already in the market.
- With regard to the substance-based assessment, the NVR still follows a product-based approach, similar to the Directive. It must be remarked that the NVR also requests an in-depth analysis of the applicability of a substance-based approach in article 156. This article requires the EC to explore the feasibility and usability of an active substance-based review system (i.e., "monographs system") and any other potential alternatives for improving the ERA of VMPs.

In summary, comparing both legislations, it can be seen that the NVR achieves some advances in what refers to the ERA of legacy products or the consistency of the assessments (i.e., substance-based assessment vs product-based assessment). These advances are, however, discreet and somehow subject to the interpretation and the willingness of the NCAs. The NVR keeps the possibility of further improving the approach to those two important aspects of the ERA by requesting the EC to carry out a feasibility study on a monograph system or an alternative to it.

In the following section "performance of the current and forthcoming legislation in environmental aspects and regulatory burdens", we will analyze in depth the performance of the Directive and the NVR in relation to the legacy products and the consistency of the assessments (substance-based instead of product-based). We consider these two as crucial items for achieving the goal of ensuring the highest environmental protection. When carrying out this analysis, besides the environmental protection, we will take into account the impact on the administrative burden, as it is a major aim of every EU legislation.

In the section "Proposals for the development of a monograph system," we will explore the possible basic layouts that a monograph system (as requested by article 156 of the NVR) might have.

In the section "Further considerations for the development of a monograph system," we will briefly discuss additional considerations of a potential monograph system (e.g., publicity of environmental information, experiences of other chemical's frameworks) and analyze advantages and disadvantages of the system.

PERFORMANCE OF THE CURRENT AND FORTHCOMING LEGISLATION IN ENVIRONMENTAL ASPECTS AND REGULATORY BURDENS

In our view, considering environmental considerations presented in the previous section, the legislation on VMPs should ensure three basic requirements: (i) the environmental risks of every VMP in the market are known, (ii) the technical requirements of the authorization dossier do not have an unnecessary regulatory burden, and (iii) it should allow the regulators to achieve consistent and reliable conclusions, that is, the conclusions of the assessment

 DOI: 10.1002/ieam.4431

should be identical for those products with equal formulations and indications. The fitness of the Directive/2001/82/EC and the NVR to those three requirements is analyzed below.

Are the environmental risks of all VMPs in the market known?

As indicated above, one of the requirements of the ERA legislation of VMPs would be that the environmental risks of all VMPs in the market are known, following the assessment under the current guidance (i.e., VICH GL6, GL38, and EMA supporting guideline). Directive 2001/82/EC requires an ERA to be performed for all new MAs, independent of the type of application procedure followed (Table 4). However, the overall capacity of the Directive to identify the environmental risks of all VMPs in the market might be described as very low. This is because the completeness and accuracy of the ERA will vary depending on the date of the product's authorization for VMPs already in the market. This is due to the technical requirements of the ERA evolving over time. For VMPs authorized before the "Note for guidance on environmental risk assessment for veterinary medicinal products other than GMO-containing and immunological products" (EMEA/CVMP/055/96) came into force in 1998 (Table 1), an ERA will not have been performed; however, some of these legacy products are still in the market today. The ERA of those legacy products could be reviewed or updated by means of a so-called "Union interests" referral procedure according to article 35 of the Directive 2001/82/EC. These procedures cannot completely solve the problem, as they are not as frequently performed as desired, because the triggering of referrals depends on the identification of a specific risk for the environment and the willingness of an NCA to initiate the process.

In regard to the NVR, it includes provisions enabling the harmonization of SPCs of nationally authorized VMPs and their generics (articles 70–72). It allows for the retrospective performance of an ERA for reference products authorized before October 1, 2005 in case they may pose a risk to the environment. Although these provisions place the NVR closer to a strong legislation in terms of knowledge of the environmental risks of all VMPs when compared with Directive 2001/82/EC, a systematic procedure for the revision of the ERA of legacy products is still not foreseen, as the SPC harmonization procedure depends again on the resources and willingness of the NCAs. The "Union interest" referral procedure according to article 35 of Directive 2001/82/EC is still available, although now under article 83 of the NVR. This procedure can thus still be triggered to review the ERAs of authorized VMPs and consequently ensure ERA harmonization between products in the market; however, the initiation of this procedure again largely depends on the willingness of competent authorities to do so, that is, article 83 referrals are not systematically activated procedures. Therefore, although additional tools are provided by the NVR to increase the knowledge of the environmental risks of all VMPs in the market, some gaps still remain.

Are the current and forthcoming legislations proportional?

In our view, the application of the legislation should achieve the highest environmental protection without posing unnecessary regulatory burdens for both authorities and applicants. However, the provision that an ERA has to be presented for all new MAs regardless of the authorization route included in Directive 2001/82/EC entails that redundant evaluations of the fate, behavior, and ecotoxicity of the same active substance are performed for every VMP actually containing the compound. It must be stressed that although the ERA of VMPs is "product-based," the complete fate, behavior, and ecotoxicology data package required is based on the active ingredient and not on the formulated product. The current requirements under the Directive imply that a full new data package should be submitted for each VMP, independently of how many times the main active ingredient has been assessed before for other VMPs containing the same substance. The consequence is a considerable expense in terms of financial and human resources incurred both by applicants (who have to provide the studies and the ERA) as well as authorities (who have to assess them). The proportionality of the Directive is low.

However, the NVR stipulates in article 18(7) that the performance of an ERA is not required for generic products whose reference product was authorized after October 1, 2005. This implies a certain reduction of the workload, as not all generic medicines have to undergo a compulsory evaluation of their environmental impact anymore. The ERA of generics authorized under the NVR will, therefore, be aligned with the ERA of their respective reference products (if they were authorized after 2005). This can be considered a step forward in terms of administrative burden. As mentioned above, generics of a reference product authorized before 2005 might still require the performance of an ERA and it is not known yet how often and under which circumstances an ERA will be requested.

Is the ERA legislation of VMPs consistent and reliable?

In our opinion, a reliable ERA legislation for VMPs would be one that delivers equal conclusions for all VMPs based on the same active substance, irrespective of the legal basis (Table 4) underlying the authorization. For Directive 2001/82/EC, the final conclusions on the ERA are dependent on the specific data set supplied for the active substance of each VMP and on the predicted exposure of each product. Although the latter is specific for each VMP and its target species, dosage, and so forth, the conclusion on the active substance data set assessment should be the same for all products with identical active ingredients. Each product has its own data sets, leading in some cases to different conclusions regarding the risk characterization of identical VMPs (Table 4). This situation can cause the removal of certain indications or, in the worst case, the refusal of the MA of the VMPs in certain MSs, whereas for other identical VMPs, no concerns might have been found. For the same reasons mentioned above, different risk warnings,

environmental properties, and risk mitigation measures (RMMs) appear in the SPCs of VMPs containing the same active substance, creating an undesired lack of harmonization across the EU. This could be solved by means of a "Union interests" referral procedure according to article 35 of Directive 2001/82/EC. Nevertheless, as indicated above, these procedures are not as frequently performed as desired, as their triggering depends on the identification of a specific risk for the environment and the willingness of an NCA to actually initiate the process. Therefore, a low level of consistency and reliability is achieved under the Directive.

In the NVR, the conclusions of the ERA, SPC warnings, and RMM are still product-specific factors that depend on an assessment based on the data set provided for the active substance and the exposure features of the product. Those generics using a reference product authorized before 2005 may still have to provide their complete and proprietary ERA. The conclusions on these generic products will be based on the specific data set provided, and therefore the ERA and the corresponding assessment might not necessarily arrive to equal environmental conclusions, risk warnings, and RMM as the reference product. Those products authorized during the two-year gap between the enforcement of the VICH GL38 and the EMA guidelines (i.e., between 2005 and 2007) will not be compliant with the guidance update carried out after 1/10/2005, particularly in what refers to exposure calculation.

The significance of an updated ERA for the authorization under the NVR and its impact on the assessment reliability needs consideration. Scientific and technical guidance for ERA of VMPs has been continuously updated since the adoption of the VICH GL38 guideline in 2005. New and updated reflection papers and guidelines have been adopted as needed to accommodate scientific and technical progress in the field, as detailed in Table 2. Important conceptual changes in the ERA for VMPs have been introduced after October 1, 2005. These changes have several important implications. First, before the current "Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38" (EMEA/CVMP/ERA/418282/2005 Rev. 1 Corr.; EMA, 2016) came into force in March 2007, exposure calculation was not standardized and the default values for exposure calculation were significantly different. Consequently, the ERA for products assessed before that date may have stopped at Phase I. If assessed in accordance with current guidance, these products might require a Phase II assessment with a full data package. In addition, VMPs undergoing a Phase II ERA before 2007 could have had a non-guideline-compliant exposure calculation applied, resulting in a different risk characterization, that is, ERA conclusions and RMM might significantly differ from what would be concluded today.

Under the NVR, the authorization of a VMP may be refused if it contains an active substance classified as PBT/vPvB (persistent, bioaccumulative, and toxic/very persistent and very bioaccumulative). However, the assessment of the PBT/vPvB status of an active principle was not mandatory until 2007, and a fully detailed guidance on how to perform such an assessment was only available from April 1, 2016 ("Guideline on the assessment of persistent, bioaccumulative and toxic [PBT] or very persistent and very bioaccumulative [vPvB] substances in veterinary medicinal products" [EMA/CVMP/ERA/52740/2012; EMA, 2015]). The ERA performed for VMPs containing such substances and authorized before that date would not necessarily fulfill assessment criteria as required by current or future legislation.

Before 2018, the assessment of groundwater pollution was solely based on exceeding pre-determined limit values without clear reference for VMPs on how to proceed if these limits are exceeded. The EMA/CVMP/ERA/103555/2015 guideline (EMA, 2018) that came into force in 2018 gives details on how to perform the risk assessment for groundwater ecosystems and for drinking water if the triggers are exceeded.

By applying the trigger date of October 1, 2005, important ERA criteria might not be considered. To be more reliable and consistent, the NVR should allow for the ERA of products authorized after that date to be reviewed and harmonized in accordance with the current guidelines.

Overall reflection

To summarize, the ERA provisions included in Directive 2001/82/EC (i) do not allow the systematic review of the environmental risks of all the VMPs in the market, (ii) impose a high regulatory burden for applicants and NCAs by requiring an ERA for every single VMP placed in the market (i.e., low level of proportionality), and (iii) lack harmonization due to repeated assessment and variety of data sets (i.e., low level of consistency and reliability).

In relation to the NVR, there are some advances in terms of proportionality of the regulatory burden, but the issues related to the lack of awareness of the environmental risks of all the VMPs in the market and the issues related to consistency and reliability remain.

It is important to note that the NVR provides yet another provision that could become an important tool to address all these shortcomings. When article 156 on the review of the ERA requirements comes into force in January 2022, the EC will present to the European Parliament and the Council a feasibility study of an active substance-based review system (the so-called "monographs") or other potential alternatives for the environmental risk assessment of VMPs.

The scope, content, and uses of a monograph system are not yet defined, but in our view, it should aim at covering the gaps identified above to improve the ERA legislation. This will increase environmental protection and reduce the administrative burden. In the following sections, we make two proposals for a monograph system with different levels of complexity. For each of the two systems proposed, the following features will be considered: environmental risk knowledge (understood as the capacity of gaining environmental information of legacy products), proportionality (the implications on regulatory burdens of the monograph

 DOI: 10.1002/ieam.4431

system considered), and consistency and/or reliability (the ability to achieve equal ERA conclusions and RMM for equal VMPs).

PROPOSALS FOR THE DEVELOPMENT OF A MONOGRAPH SYSTEM

Although the NVR does not cover all the gaps detailed above, it is important to note that Article 156 does provide the opportunity to investigate the feasibility of the future performance of ERAs based on the properties of the active substance ("monographs") or any other potential alternatives. This would constitute an opportunity to cover the shortcomings identified above and to obtain a more protective, proportional, and consistent regulation of VMPs.

In the following paragraphs, we will explore the advantages and disadvantages of an active substance-based review system. Our aim is rather to focus on high-level principles that might help establish the steps needed for a practical, functional monograph system that will be able to address the issues identified.

It is important to note that although the ERA of VMPs is "product-based," the emission pattern only concerns the "active substance," as most of them first pass through the animal to which it is administered (with the exception of certain topical VMPs or those aquaculture VMPs added directly to water). The most significant environmental exposure results from the excretion of the active substance as parent compound and/or its metabolites. It should be also considered that the intrinsic properties, fate, behavior, and ecotoxicity endpoints are inherent to the active substance, independent of the product containing the substance. The specific characteristics of each formulated product will only have an influence on the environmental exposure calculations, not on the active substance endpoints. The parameters such as indications of use, target species, the amounts to be administered, or the administration route are only used for exposure calculations. Once the endpoints of the active substance have been determined, the test results can be applied to all products containing the substance, independently of the specific characteristics of the product (i.e., use, dose, or target animal). With this in mind, the first step to study the usefulness of a monograph system would be to address the structure and composition of a monograph dossier, for which we propose two options: basic and enhanced approach.

Basic approach

In this approach, the monograph would be based on a harmonized and agreed-upon assessment between all the NCAs of a tier IIA data set, as stipulated in VICH GL38 as well as in accompanying EMA guidance (EMA/CVMP/ERA/418282/2005-Rev.1- Corr.1; EMA, 2016) and subsequent updates (if any). No risk characterization (exposure and risk calculation) would be performed. The outcome of this monograph layout would be a list of endpoints acceptable to all MSs. The monograph for a specific active substance would only be produced if at least one indication for one target species would be above a certain threshold value and thus required to progress into Phase II of VICH GL38. Those VMPs containing active substances that would not require an assessment beyond Phase I would thus be considered safe for the environment due to the low expected exposure and no monograph would be needed for such compounds. In any other case, the applicants could then refer to the active substance monograph containing data on endpoints and, using those endpoints, perform the necessary ERA for each VMP containing the substance in question during the authorization procedure.

This approach entails the following advantages in terms of environmental risk knowledge, proportionality, and consistency and/or reliability:

Environmental risk knowledge: A monograph system is not expected to directly increase the environmental risk knowledge of all authorized VMPs, as it would not imply the performance of an ERA for legacy products. However, once the monograph is available, it might be easier to develop a revision procedure for those VMPs containing the active substance in question, including legacy products for which no ERA at all has been performed (i.e., those authorized before 1997 [Table 1]).

Proportionality: In terms of administrative burden, the workload for NCAs would be reduced as they would not have to repeatedly evaluate the fate and ecotoxicity data for VMPs containing the same active principle for each application. The exposure and risk assessments would still have to be assessed in each VMP authorization procedure. For the same reasons, the applicants' workload would be also reduced. However, the conditions for providing the data and accessing the monographs should be carefully defined so as to ensure a fair treatment of all applicants using the active substance monograph for the preparation of the required ERA.

Consistency and/or reliability: By using this monograph approach, consistency and reliability of the ERA conclusions would be increased, because certain key aspects (i.e., ecotoxicological endpoints) of the ERA would have been previously agreed upon by all MSs. However, the final conclusions of the ERA would still depend on the specific use of each authorized VMPs (i.e., use, dose, or target animal) and the judgment of the different NCAs. It is reasonable to expect harmonization of the ERA conclusions if they are based on an EU-wide accepted data set as described in the monograph. It is important to note that currently some of the differences observed in the conclusions for equal or similar products are due to different data sets submitted by the applicant for each product.

However, it has to be noted that depending on the risk profile, the performance of higher-tier studies (tier IIB or IIC) might be required, and these are not foreseen in this "basic approach." However, if it is known in advance which higher tier studies would be required (based on the authorities' experience or scientific data), they could be submitted together with the basic tests (tier IIA) for a uniform assessment to be performed. Otherwise, higher tier studies (tier IIB or

IIC) would be evaluated on a case-by-case basis, which might entail a reduction in Consistency and/or reliability, as not all the endpoints would have been agreed by the NCAs beforehand.

Enhanced approach

With an enhanced approach, the monograph would include a complete risk assessment, that is, basic studies (tier IIA) as mentioned above, in addition to a risk characterization as well as, if applicable, higher tier studies (tier IIB or IIC) and RMMs. This monograph design should contain data on all the indications, application forms, and target species in which the active substance could be used. This way, it would cover every possible scenario of the use of the VMP, and consequently, the conclusions and RMMs previously agreed upon by NCAs would be applied to every VMP authorized afterward. Alternatively, the ERA of the monograph could be carried out using the highest authorized or intended exposure, considering that any lower exposure would have lesser effects on the environment. In this case, care should be taken to address any effects of the active substance related to target species specificities (e.g., metabolism, excretion profile, degradation in manure) that might have an impact on exposure calculation refinement. It should also be considered that the RMMs might not always be transferable among different farming systems.

The "enhanced approach" has the following advantages in terms of knowledge of the environmental risks, proportionality, and consistency and/or reliablity:

Environmental risk knowledge: As applicable to the "basic approach," the "enhanced approach" itself would not increase the environmental risk knowledge unless a systematic review of legacy products was required after the monograph publication. As indicated above, once a monograph for a certain substance is published, it might be easier to perform a systematic revision of the ERA of legacy VMPs containing that substance. The revision would be even more straightforward as the RQ calculation and potential RMMs would already be included in the monograph's conclusions.

Proportionality: The NCAs' and applicants' workload would be reduced considerably as the monograph would be directly referred to during the authorization procedure without needing to provide additional environmental information.

Consistency and/or reliability: By using the enhanced monograph approach, consistency and/or reliability of the ERA legislation is expected to be complete, as with taking this approach, the monograph would not only include data on relevant endpoints but also a complete risk assessment accepted by all NCAs. Warnings and potential RMMs included in the SPC would be the same for the reference product as well as all generics thereof.

It is important to note that not only the performance of VMP approval procedures by NCAs would greatly benefit from a monograph system, but applicants would also profit from a more predictable and transparent procedure, with (at least) the conclusions drawn from fate and ecotoxicity data being the same for all products with the same active ingredient. The availability of a "basic" monograph would reduce the applicants' economic expenses by eliminating the need for the submission a complete data set for each product containing the substance. This cost reduction could be even higher in the "enhanced approach," as for some generic applications, a complete and agreed-upon ERA would be published available.

FURTHER CONSIDERATIONS FOR THE DEVELOPMENT OF A MONOGRAPH SYSTEM

The development of a monograph system appears to be a good opportunity to improve the coherence and scientific quality of ERAs performed for VMPs. The process requested by article 156 of the NVR has already started. In April 2020, the EC launched a call for tender to study the feasibility of such monograph system (SANTE/2020/OP/0001), so the procedure is ongoing.

In this section, we will reflect on additional issues beyond those already discussed (i.e., environmental risk knowledge, proportionality, and consistency and/or reliability) and that we consider useful for the development of a monograph.

The Aarhus Convention and the Environmental Information Directive

The EU has been a party to the Aarhus Convention since May 2005. The Convention has three main "pillars": access to information, public participation, and access to justice. The first pillar is implemented in the EU with the Environmental Information Directive (EID) Directive 2003/4/EC that reflects on the right of everyone to receive environmental information that is held by public authorities. Regarding VMPs, in the last few years, the environmental information has been made public in the form of Public Assessment Reports (PuARs) that are published by the NCAs. Nevertheless, the PuARs are only available for the most recently authorized VMPs and they are not systematically applied by all NCAs. A monograph system would allow satisfaction of the commitments required by the EU in the Aarhus Convention and compliance with the EID by making public the environmental information assessed during the procedure of developing the monographs.

Sources of information for a monograph system

It is important to note that, considering VICH Phase I guideline, only some of the active substances used in VMPs would require a Phase II assessment. Some of these environmentally relevant substances have already been assessed in the context of an MA procedure. This implies that environmental information according to current VICH and EMA guidance is available for many of these substances (i.e., the ERA has been performed according to the current state-of-the-art procedures). This information could be gathered to produce a monograph on an active substance without requiring the generation of new environmental fate and ecotoxicity data. However, neither the data

 DOI: 10.1002/ieam.4431

package submitted with the dossiers nor the PuAR can be used at the moment by other applicants to authorize a VMP. With this in mind, competent authorities (CAs) and marketing authorization holders (MAHs) should closely collaborate to develop a system to share information that benefits all stakeholders. For instance, a consortium representing MAHs might be a good option to provide all available data, which could be then assessed in a centralized manner acceptable to all NCAs across the EU.

Impact on the availability of VMPs

There are still some active substances for which no updated environmental information is available. Some of these active substances belong to VMPs intended for limited markets where less economic profit can be obtained by the MAHs (minority species such as rabbits, aquaculture species, or goats, or infrequent diseases). These VMPs pose a big challenge for the development of a monograph system, as the resources of MAHs of such products are often limited and the performance of required studies might often not be considered financially viable. There is no information on how many products are actually affected by this scenario; however, the implementation of a monograph system might have a negative influence on the availability of VMPs in such cases. This is a major issue that should be carefully considered, as the availability of VMPs is a matter of utter importance addressed by both the Directive as well as the NVR.

Update of the monographs

A monograph should be considered a "living document" continuously adapted to the current state-of-the-art information and changes in the MA that could impact the exposure calculation (e.g., new target species, changes in dose or indications). Therefore, once the monograph for an active substance is established and published, a periodical revision should be undertaken to ensure that the monograph is up to date.

ADVANTAGES AND CHALLENGES OF A MONOGRAPH SYSTEM

Considering all the above, the adoption of a monograph-based ERA would entail at least the following advantages:

1. Reduction of workload for applicants and authorities once a monograph is available.
2. Harmonization of ERAs among VMPs based on the same active ingredient.
3. Consistent outcome of PBT/vPvB assessment.
4. Increased transparency and better knowledge of the active substances marketed.
5. More reliable ERA conclusions.
6. Reduced uncertainty for the applicants during the procedure of authorization of new VMPs, as the ERA provided in the dossier would already be agreed upon by all European NCAs.
7. Reduction of costs needed to generate an MA dossier.
8. Better alignment with the EU legislation for the protection of animals used for experimental purposes (the so-called "Three Rs principles" due to less testing required.
9. Better alignment with the principles of "Green Chemistry" due to the reduced number of tests carried out with the consequent reduction of the use of hazardous chemicals such as organic solvents and radiolabeled material.
10. Benefits for environmental monitoring schemes in terms of defining priorities and better knowledge of environmental fate.
11. Improved collaboration and communication with other regulatory frameworks.

In summary, the development of a monograph system (independently of the approach considered) would entail an increase in the knowledge of the environmental risks of all VMPs. This knowledge would be the same for all European MSs that implies a better use of the products in Europe and the refusal of some MA, if necessary. Furthermore, monitoring approaches would be focused on those substances that suppose the highest risk, prioritizing the efforts. And last, a harmonized assessment will improve the communication and collaboration with other regulatory frameworks.

However, before a fit-for-purpose monograph system can be established, the authorities would face at least the following challenges:

1. Legislation and guidance development: Precise legal specifications and broad support from stakeholders and NCAs would be required.
2. The monograph system should not imply reduced availability of VMPs.
3. Clear indications on the responsibilities to perform the assessment between NCAs and a clear timetable for reaching conclusions.
4. Not all substances can be assessed at the same time. A risk-based system should be used for prioritization.
5. Financial resources are needed to develop such a system.
6. Clear and proportionate rules of access to the monographs to ensure that the system does not distort the market.
7. Clear rules on whom should provide the information included in the monograph.
8. Deciding on how to achieve the EID objectives and make available the monograph information to general public, regulators, and scientists.

CONCLUSIONS

The NVR constitutes an important step forward with respect to the current legislation (Directive 2001/82/EC). However, some gaps related to the harmonization and review of legacy products still exist regarding the ERA of such products. The analysis of the efficacy of the current and

forthcoming legislation to protect the environment and reduce the regulatory burden is very helpful to pinpoint the weaknesses and strengths of both. In our view, that efficacy can be summarized in the following three features: environmental risk knowledge, proportionality, and consistency and/or reliability. Considering these features, the current and future legislation is not as protective, proportional, and consistent as desired. The development of a monograph system can be a good opportunity to address these deficiencies.

When designing a monograph system, it should be considered that (i) the fate and behavior, as well as ecotoxicological endpoints, are inherent to each active substance, independently of the formulated product where they are used, and (ii) the VMP formulation and indications will have an impact only on exposure and therefore on the risk characterization. These two considerations define the scope of different monograph systems, that is, a monograph that provides a set of agreed-upon endpoints for each active substance or a monograph that provides the endpoints and risk characterization of each product containing the active substance.

Independently of the design of monograph decided, a monograph system will solve (to a different extent, depending on the scope chosen) the shortcomings identified in the legislations and provide additional benefits related to, for example, transparency or animal welfare. Nevertheless, the system will face numerous challenges that could affect, for example, the availability of VMPs. For that reason, any system chosen should be carefully defined and agreed upon by the relevant stakeholders and NCAs

ACKNOWLEDGMENT

The authors wish to thank Silke Hickmann, Susanne Schmitz, Michael Empl, María Victoria Carapeto García and Cormac Feeney for their comments on an earlier version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agency with which the authors are affiliated.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

REFERENCES

Directive 91/271/EC. (1984). Council Directive of 21 May 1991 concerning urban waste water treatment. *Official Journal of the European Communities*, *L135*, 40–52.

Directive 92/18/EEC. (1992). 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. *Official Journal of the European Communities*, *L97*, 1–23.

Directive 2001/82/EC. (2001). 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. *Official Journal of the European Communities*, *L311*, 1–110.

Directive 2003/4/EC. (2003). Directive 2003/4/EC of the European Parliament and of the Council of 28 January 2003 on public access to environmental information and repealing Council Directive 90/313/EEC. *Official Journal of the European Union*, *41*, 26–32.

Directive 2004/28/EC. (2004). Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products. *Official Journal of the European Communities*, *L136*, 58–84.

Directive 2008/105/EC. (2008). Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council. *Official Journal of the European Union*, *L348*, 84–97.

EC. (2018). Commission Implementing Decision (EU) 2018/840 of 5 June 2018 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council and repealing Commission Imprementing Decision (EU) 2015/495. *Official Journal of the European Union*, *L141*, 9–12.

EC. (2019a). Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of Regions. The European Green Deal (COM(2019) 640 final). European Commission.

EC. (2019b). Communication from the Commision 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). European Commission.

EC. (2020a). Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of Regions. A Farm to Fork Strategy for a fair, healthy and environmentally-friendly food system (COM(2020) 381 Final). European Commission.

EC. (2020b). Commission Implementing Decision (EU) 2020/1161 of 4 August 2020 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council. *Official Journal of the European Union*, *L257*, 32–35.

EMA. (2000). Guideline on environmental impact assessment (EIAs) for veterinary medicinal products (VMPs)—Phase I (CVMP/VICH/592/98-FINAL). European Medicines Agency.

EMA. (2004). Guideline on environmental impact assessment for veterinary medicinal products Phase II (CVMP/VICH/790/03-FINAL). European Medicines Agency.

EMA. (2015). Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products (EMA/CVMP/ERA/52740/2012). European Medicines Agency.

EMA. (2016). 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). European Medicines Agency.

EMA. (2018). Guideline on assessing the environmental and human health risks of veterinary medicinal products in groundwater (EMA/CVMP/ERA/103555/2015). European Medicines Agency.

EMEA. (1998). Environmental Risk Assessment for veterinary medicinal products other than GMO-containing and immunological products (EMEA/CVMP/055/96-FINAL). European Medicines Agency.

NtA 6C. Notice to Applicants Veterinary Medicinal Products Volume 6C. (2009). Guidance on the assessment of environmental risks of veterinary medicinal products. European Commission.

Organisation for Economic Co-operation and Development (OECD). (2019). Pharmaceutical residues in freshwater: Hazards and policy responses. https://doi.org/10.1787/22245081

Regulation (EC) No 726/2004. (2004). Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *Official Journal of the European Union*, *L136*, 1–33.

Regulation [EC] 1107/2009. (2009). Regulation 1107/2009/EC of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. *Official Journal of the European Union*, *L309*, 1–50.

Regulation (EU) 528/2012. (2012). Regulation (EU) 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. *Official Journal of the European Union*, *L167*, 1–120.

Regulation (EU) 283/2013. (2013). Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance. *Official Journal of the European Union*, *L93*, 1–84.

Regulation (EU) No. 284/2013. (2013). Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance. *Official Journal of the European Union*, *L93*, 85–152.

Regulation (EU) 2019/6. (2018). 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. *Official Journal of the European Union*, *L4*, 43–167.

SAICM/ICCM.4/7. (2015). Implementation towards the achievement of the 2020 goal of sound chemicals management: Emerging policy issues and other issues of concern: Proposal on environmentally persistent pharmaceutical pollutants as a new emerging policy issue. In: International Conference on Chemicals Management Fourth session. Geneva.

SANTE/2020/OP/0001. Feasibility study of an active-substance-based review system ('Monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products. https://etendering.ted.europa.eu/cft/cft-display.html?cftId=6192

