

Article

Risk Mitigation Measures: An Important Aspect of the Environmental Risk Assessment of Pharmaceuticals

Markus Liebig^{1,†}, Carolin Floeter^{2,†}, Thorsten Hahn³, Wolfgang Koch⁴, Andrea Wenzel^{5,†} and Jörg Römbke^{1,†,*}

¹ ECT Oekotoxikologie GmbH, Boettgerstrasse 2-14, 65439 Floersheim/Main, Germany; E-Mail: garcia-liebig@alice.de

² Hamburg University of Applied Sciences (HAW), Lohbrügger Kirchstraße 65, 21033 Hamburg, Germany; E-Mail: carolin.floeter@science-and-law.de

³ Fraunhofer Institute for Toxicology and Experimental Medicine—ITEM, Nikolai-Fuchs-Str. 1, 30625 Hannover, Germany; E-Mail: torsten.hahn@tu-braunschweig.de

⁴ Federal Environment Agency (Umweltbundesamt), IV 2.2, Wörlitzer Platz 1, 06844 Dessau-Rosslau, Germany; E-Mail: wolfgang.koch@uba.de

⁵ Fraunhofer Institute for Molecular Biology and Applied Ecology—IME, Auf dem Aberg 1, 57392 Schmallenberg, Germany; E-Mail: andrea.wenzel@ime.fraunhofer.de

† These authors contributed equally to this work.

* Author to whom correspondence should be addressed; E-Mail: j-roembke@ect.de; Tel.: +49-6145-956450; Fax: +49-6145-956499.

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Abstract: Within EU marketing authorization procedures of human and veterinary medicinal products (HMP and VMP), an environmental risk assessment (ERA) has to be performed. In the event that an unacceptable environmental risk is identified, risk mitigation measures (RMM) shall be applied in order to reduce environmental exposure to the pharmaceutical. Within the authorization procedures of HMP, no RMM have been applied so far, except for specific precautions for the disposal of the unused medicinal product or waste materials. For VMP, a limited number of RMM do exist. The aim of this study was to develop consistent and efficient RMM. Therefore, existing RMM were compiled from a summary of product characteristics of authorized pharmaceuticals, and new RMM were developed and evaluated. Based on the results, appropriate RMM were applied within the authorization procedures of medicinal products. For HMP, except for the

existing precautions for disposal, no further reasonable measures could be developed. For VMP, two specific precautions for disposal and 17 specific precautions for use in animals were proposed as RMM.

Keywords: authorization; environmental risk assessment; medicinal products; risk mitigation

Abbreviations: Ad, number of days of treatment; AMG, Arzneimittelgesetz (German Pharmaceuticals Act); BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (German Federal Office of Consumer Protection and Food Safety); BW, animal body weight; D, daily dose of the active ingredient; DüV, Düngeverordnung (German Fertilization Ordinance; implementation of the Nitrate Council Directive in German law); EEC, European Economic Community; EMA, European Medicines Agency; EPAR, European public assessment report; EPV, eco-pharmacovigilance; ERA, environmental risk assessment; ERBA, environmental risk-benefit assessment; EU, European Union; Fh, fraction of herd treated; HMP, human medicinal product; PEC, predicted environmental concentration; PNEC, predicted no effect concentration; RMM, risk mitigation measure; RQ, risk quotient; SD, stocking density; SmPC, summary of product characteristics; VICH, International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products; VMP, veterinary medicinal product.

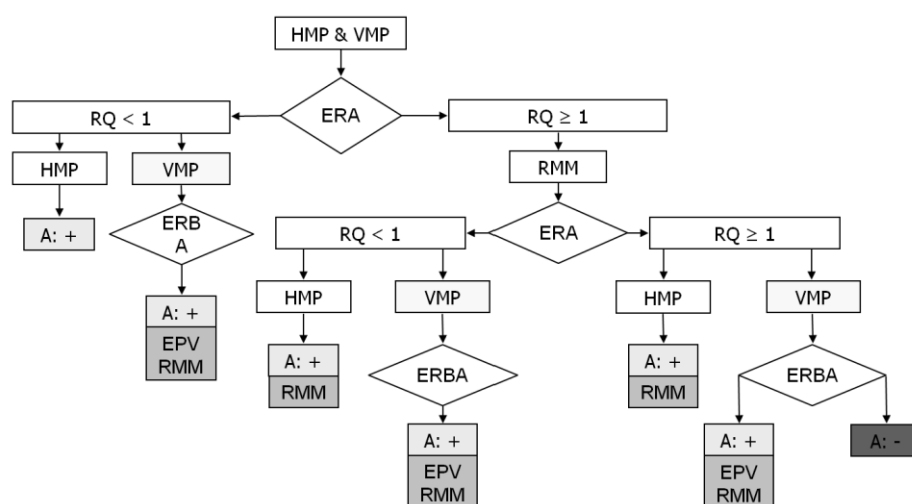
1. Introduction

When seeking authorization for placing medicinal products on the market within the European Union (EU), applicants have to provide environmental risk assessments (ERAs) according to EMA [1] for human medicinal products (HMPs) and according to VICH [2,3], complemented by EMA [4], for veterinary medicinal products (VMPs). If the ERA of a VMP indicates an unacceptable risk to the environment, *i.e.*, the risk quotient (RQ) consisting of the ratio of PEC (predicted environmental concentration) to PNEC (predicted no effect concentration) is equal to or larger than one, and/or the risk-benefit balance is negative, *i.e.*, the therapeutic benefit is outweighed by risks to the environment, safety or efficacy, the authorization can be refused [5]. An exemplary performance of an ERA for a VMP is provided by Liebig *et al.* [6]. Risk mitigation measures (RMMs) can be applied to improve the prevention of exposure and the protection of the environment and, in the case of risk indication within the ERA (*i.e.*, $RQ \geq 1$), to reduce the RQ with a follow-up step of the RQ calculation (Figure 1). For example, such an RMM could be the prolonged storage time of slurry before spreading on arable land. Consequently, this RMM would allow for extended biodegradation of the medicinal product and its residues and, hence, lower the RQ in the ERA.

When a medicinal product is marketed, information on adverse reactions that may occur after the administration of a pharmaceutical product is gathered using the concept of pharmacovigilance [5,7]. For VMPs, the pharmacovigilance includes the observation of environmental risks (eco-pharmacovigilance) and, thus, can be the legal background to establish the effect and exposure monitoring programs (AMG, Arzneimittelgesetz (German Pharmaceuticals Act) [8]). Challenges and concepts for the implementation of ecopharmacovigilance are presented, *e.g.*, in Daughton and

Ruhoy [9] and Holm *et al.* [10]. Although an environmental risk-benefit assessment and refusal of authorization due to environmental concerns are not foreseen for HMPs, RMMs can also be applied to human pharmaceuticals [8,11]. In Figure 1, the various options are shown when RMMs can be applied as part of the overall evaluation of the environmental concerns of HMPs and VMPs.

Figure 1. Schematic flow chart showing the options to apply risk mitigation measures as part of the evaluation of environmental concerns of human (HMP) and veterinary medicinal products (VMP). Environmental concerns are addressed by calculating the risk quotient (RQ: the ratio of predicted environmental concentration to predicted no effect concentration), by conducting an environmental risk-benefit assessment and by improving the safety of marketed products through eco-pharmacovigilance. The scheme reflects provisions contained in [5,7] and AMG, Arzneimittelgesetz (German Pharmaceuticals Act) [8].



ERA: environmental risk assessment
 A: authorization: (+) granted; (-) refused
 ERBA: environment risk-benefit assessment
 EPV: eco-pharmacovigilance
 RMM: risk mitigation measure

Applicants and competent authorities are interested in a set of recommended and appropriate RMMs from which, when considering a specific product, the adequate RMMs can be chosen either to shift the risk quotient below one and/or to generate a positive risk-benefit balance. The existing guidelines for ERAs of VMPs [1,4], as well as the guidelines for preparing the summary of product characteristics (SmPC) [12,13], provide a rather limited number of exemplary RMMs. In addition, Montforts *et al.* [14] showed that for VMPs existing and so far applied, RMMs are controversial, and their efficiency is not confirmed in all cases. Depending on the marketing authorization procedure (decentralized, centralized, mutual recognition or national [15]), the year of authorization and the reference member state, RMMs for existing products with the same active ingredient can differ significantly.

In principle, RMMs can be related to the whole lifecycle of a pharmaceutical product. However, measures within the authorization procedure related to intrinsic properties of the active ingredient or related to sewage treatment techniques are not specific for a product and, thus, are not taken into account here. The objective of this study is to propose a catalogue of RMMs, which may provide

applicants and competent authorities with a useful source of appropriate and efficient RMMs to be applied within marketing authorization procedures. To this end, existing and new RMMs based on modified exposure models are evaluated using criteria related to, amongst others, efficiency, practicability and compatibility with European and/or national law.

As mentioned above, the availability of existing RMMs for HMPs is very sparse, and the possibilities to apply product specific RMMs within authorization procedures for HMPs is limited. Therefore, in the following, focus is given on RMMs for VMPs. Results of this research related to HMPs are presented in Section 5 and discussed briefly in Section 6.

Further details of the research project funded by the German Federal Environment Agency on which this article is based are provided in the final report by Liebig *et al.* [16].

2. Sources of RMMs

2.1. Compilation of Existing RMM from Authorized VMP and Scientific Literature

The databases, EudraPharm [17] and EPARs (European public assessment reports) from EMA [18] and data from BVL (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit—the German Federal Office of Consumer Protection and Food Safety [19]) were screened for active ingredients of VMPs (except of vaccines) for which either definitive (Annex I of Council Regulation (EEC—European Economic Community) No 2377/90, as amended [20]) or preliminary maximum residue limits (Annex III of Council Regulation (EEC) No 2377/90, as amended [20]) are provided; active ingredients for which any detectable residue may have adverse effects to the consumer are also taken into consideration (Annex IV of Council Regulation (EEC) No 2377/90, as amended [20]). All SmPCs referring to products containing active ingredients listed in Annex I, III and IV of Regulation (EEC) No 2377/90, as amended [20], were searched for RMM, as far as these products are authorized for food producing animals (cattle, pigs, poultry, sheep/goats, horses and fish).

Considering the impact on the environment, the guideline on SmPC [12] contains three examples of precautions for the use of VMPs, which can be described in a simplified way as:

- The product should not enter surface waters;
- Treated animals should not have access to watercourses;
- The long-term effect of the product on the population dynamics of dung organisms is unknown; therefore, it is advisable not to treat animals on the same pasture every season.

The latter of the precautions was not applied as RMM to any of the active ingredients listed in Annex I, III and IV of Regulation (EEC) No 2377/90, as amended [20], whereas the other two precautions were adjusted and applied as RMM to VMPs containing 11 different active ingredients. Additionally, the SmPC guideline [12] contains two standard phrases as precautions for the disposal of VMPs of which at least one was applied to all of the products screened; beyond the standard phrases, specific precautions for disposal were provided as RMMs to products containing 14 different active ingredients.

The general search for RMMs in the scientific literature revealed one paper [14], where the authors provided specific precautions for disposal beyond those recommended by the SmPC guideline [12]. Adler *et al.* [21] identified 22 product groups containing 109 different active ingredients for which

RMMs should be applied to reduce the environmental concentrations to acceptable levels. According to [21], the RMMs can be separated into three categories:

- Short-term measures; e.g., improved disposal and sewage treatment techniques, refusal of the spreading of contaminated manure;
- Mid-term measures; e.g., modified risk perception and risk communication of producers and consumers of medicinal products;
- Long-term measures; e.g., decisions that foster the concept of sustainable pharmacy.

However, most of the short-term and all mid-term and long-term measures are not appropriate for being applied as RMMs within marketing authorization procedures. This is due to the fact that marketing authorization procedures and RMMs applied within such procedures are product-specific, but the measures listed above are not.

2.2. Derivation of RMM Based on Exposure Models

The PNEC is one constituent of the RQ derived from ecotoxicological effects data, which are determined by conducting standardized toxicity tests. The PNEC describing inherent properties of the active ingredient cannot be modified by RMMs, whereas the other constituent of the RQ, the PEC, is the result of either simple or more complex exposure models for lower or higher tier risk assessments, respectively, as shown by the ERA guideline [4]. The model parameters necessary for calculating PECs, like physico-chemical data and degradation properties, may be experimentally determined and are considered as intrinsic, substance-specific values. Other PEC parameters related to the therapeutic dose also cannot be modified. However, PEC model parameters, like stocking density, storage time of manure or soil properties, are flexible and can be adjusted as required by developing appropriate RMMs. These derived RMMs reduce the PEC and, as a consequence, reduce the resulting RQ. Since not all exposure models from the ERA guideline [4] can be shown and discussed here, the model for calculating the $PEC_{soil\ initial}$ for the pasture animal scenario is given as an example to demonstrate the procedure of deriving RMMs based on exposure models. The parameters used in this exposure model are defined in Table 1.

$$PEC_{soil\ initial} = \left(\frac{D \times Ad \times BW \times SD \times Fh}{1,500 \times 10,000 \times 0.05} \right) \times 1000 \quad (1) *$$

* Acc. to [4], Equation (2).

Table 1. Parameters used in the exposure model for calculation of $PEC_{soil\ initial}$ (equation 1).

$PEC_{soil\ initial}$	Predicted environmental concentration in soil	-	($\mu\text{g kg}^{-1}$)
D	Daily dose of the active ingredient	From SmPC	($\text{mg kgbw}^{-1} \text{d}^{-1}$)
Ad	Number of days of treatment	From SmPC	(d)
BW	Animal body weight	Default [4]	(kgbw)
SD	Stocking density	Default [4]	(animal ha^{-1})
Fh	Fraction of herd treated	Between zero and one; default [4]	(--)
1500	Bulk density of dry soil	[4]	(kg m^{-3})
10,000	Area of one hectare	[4]	($\text{m}^2 \text{ha}^{-1}$)
0.05	Depth of penetration into soil	[4]	(m)
1000	Conversion factor	[4]	($\mu\text{g mg}^{-1}$)

D (daily dose of the active ingredient) and Ad (number of days of treatment) are values fixed by the indication and the mode of administration according to the SmPC, which should not be changed, due to therapeutic reasons. BW (animal body weight) and SD (stocking density) are given as default values for several animals or animal groups. A modification of BW, e.g., treatment only of animals with a limited body weight, is not considered realistic, due to therapeutic reasons. A modification of SD, e.g., reduction by a factor of two, would lead to a reduction of the PEC_{soil} by a factor of two. A new RMM could therefore read: “Only use at a maximum stocking density of x animals per hectare”. Whether this would be a realistic or practicable RMM is discussed later. The fraction of herd treated (Fh) is given as the default value for the different pharmaceutical product groups; for example, 100% of the herd should be treated with ectoparasiticides, whereas 30% of calves, lambs and pigs should be treated with products for diarrhea. A reduction of Fh would reduce the exposure of the product to the environment and a corresponding new RMM might read: “Only treat affected animals when required. For correct diagnosis and development of an appropriate treatment schedule, a veterinarian should be consulted. Fecal worm (worm egg) counts can be used as an indicator as to whether treatment is needed or not.” The depth of penetration into soil (default value: 5 cm) when ploughing after spreading of contaminated manure is based on the recommendation provided by the guideline [4]. Changing the depth of penetration into soil to 10 or 15 cm would lead to a reduction of the PEC_{soil} by a factor of two or three, respectively. Hence, another new RMM could read: “After spreading of manure from treated animals, soil must be ploughed to a depth of at least x cm.”

Taking into account all exposure scenarios where $PEC_{soil\ initial}$ is calculated for VMPs [4], eight parameters were identified, which theoretically can be modified and might become the source of new RMMs:

- Reduction of the fraction of herd treated;
- Reduction of the maximum applicable amount of nitrogen per hectare and year;
- Reduction of the fraction of dip entering dirty water;
- Reduction of the spreading rate for dirty water;
- Reduction of the animal turnover rate per place per year in intensively reared animals;
- Reduction of the stocking density per hectare and year in pasture animals;
- Increase of the housing factor per year from 0.5 to one for intensively reared cattle and horses;
- Increase of the depth of penetration of dung into soil (>5 cm).

Five additional parameters were found, which also could be the source of new RMMs for VMPs:

- Reduction of the highest fraction of the dose excreted in dung in one day;
- Increase of the length of time that manure is stored;
- Increase of the number of spreading events of dung;
- Avoidance of the removal of topically applied ectoparasiticides;
- Avoidance of the release to soil with a low adsorption capacity.

3. Selection of Appropriate RMMs

3.1. Evaluation Criteria for RMM

For a successful application/implementation of the RMM, the following criteria should be fulfilled by the RMM:

1. Exposure of the drug to the environment is effectively reduced (effectiveness);
2. The measure has a long-lasting effect (sustainability);
3. The effectiveness of the measure is verifiable (verifiability), e.g., by means of re-assessment of the exposure, taking the measure into account;
4. The measure is explicitly directed to the appropriate addressee (addressing);
5. Action is in accordance with good agricultural practices (practicality, for VMP);
6. The measure is proportionate (proportionality principle);
7. The measure is consistent with the relevant law(s) (legitimacy).

Criteria 1, 3, 5 and 7 were already included in the ERA guideline for VMP [4]. Criteria 1 (effectiveness), 2 (sustainability) and 3 (verifiability) are closely related to each other, in which the verifiability of the efficiency of a RMM is very important for the competent authorities. If the efficiency of a specific RMM can be verified, e.g., by re-assessing the environmental risk when considering this RMM in this re-assessment, then the authority might grant a marketing authorization on specific conditions (the RMM), or, in the worst case, refuse the authorization.

In practice, so far, it is very difficult to monitor the compliance with RMMs. In order to be accepted and applied by the farmer, veterinarian or animal holder, an RMM has to be simple, clear and comprehensible and has to be in line with (good) agricultural practices (Criteria 4 and 5). Otherwise, the measure would be fruitless, even if it results, in terms of figures, in reduced environmental risk. In regard to acceptance by the user, Criteria 6 (proportionality) is another important prerequisite for the efficacy of RMMs.

Moreover, in order to increase the transparency and acceptance of RMMs, a justification for each measure applied should be given briefly in comprehensible form in the SmPC and package leaflet, and a detailed part should be provided in the registration dossier.

3.2. Legal Boundaries for the Application of RMMs

Legal boundaries for the application of RMMs for VMPs can be summarized as follows:

1. The problem of the addressee: The addressee of the authorization to market pharmaceuticals is the pharmaceutical industry (marketing authorization holder). If an unacceptable environmental risk was identified within the marketing authorization procedure (*i.e.*, $RQ \geq 1$), which could be reduced due to THE RMM ($RQ < 1$), the marketing authorization holder receives the permission with the condition of THE RMM. However, the addressee of the RMM in practice is, in most cases, not the marketing authorization holder itself, but the user of the VMP. Thus, the RMM restricts the user in its freedom of exercise of profession, e.g., this would be the case for the RMM. “U-22: Animals [animal group] from free-range husbandry must be kept indoors during treatment and x days following treatment.” In Germany, a restriction of the

freedom of exercise of profession by the government must be based on an authorization. This is not provided in the European Directive 2001/82/EC [7] and not in the AMG [8]. Thus, in such a case, the RMM is only applicable if another European (German) regulation authorizes the state for such restrictions;

2. Principle of proportionality: The restriction of the freedom of exercise of profession by the state due to RMM needs to be proportional, *i.e.*: (1) the measure needs to be suitable for reaching the goal; (2) a milder measurement to reach the goal is not available; and (3) the measure is reasonable. The principle of proportionality was originally required in the case of restrictions of German fundamental rights by the state. In the meantime, it is also implemented in other regulations and in European legislation [22];
3. Legal consequences: If an RMM does not have the character of a recommendation (label), contempt of the RMM should have legal consequences (penalty). Neither a control of the RMM nor a penalty is provided by Directive 2001/82/EC [7] nor the AMG [8,23].

Concerning VMP and their residues, the application of slurry on agricultural land is the main entrance pathway into the environment. The RMM for the use of VMP should be consistent with the relevant laws to become an acceptable part of the agricultural practice. Therefore, the relevant legislation for the management of farm-produced fertilizers, regardless of the use of VMP, are summarized in the following using the example of the German legislation.

The European Nitrate Council Directive 91/676/EEC [24] aims to protect water quality across Europe by preventing nitrates from agricultural sources from polluting ground and surface waters and by promoting the use of good farming practices. The Nitrate Council Directive [24] is implemented in German law as “Düngeverordnung” (DüV) [25]. Relevant regulations regarding nitrogen fertilization management are laid down in Appendix III of the Directive, for example:

- Periods when fertilization is prohibited;
- Minimum storage capacity for livestock manure (at least six months; use only when the crop needs nutrients) according to national administrative regulations [26] and local ordinances;
- Rules to control the spread of nutrients near water or on slopes, to reduce the risk of contamination, e.g., by immediate incorporation of the applied slurry into the soil and under consideration of nitrogen (N) balance between nitrogen added to the soil (e.g., mineral fertilizer, livestock manure, *etc.*) and nitrogen removed from the soil in crops. The prevention of excessive levels of nutrients on farmland is a binding principle of the Good Agricultural Practices as laid down in the DüV [25]. A breach of this requirement would be considered as an administrative offence;
- A limit of 170 kg nitrogen per hectare per year (in justified exceptional cases, higher amounts are possible upon application).

In cases of agricultural soil use, the obligation of the German Federal Soil Protection Act [27] to protect or restore the functions of the soil on a permanent sustainable basis shall be fulfilled by good agricultural practices, including site-specific management of agricultural land. Besides the introduction of environmental quality standards for pharmaceutical substances (VMP and HMP) in surface and groundwater, reducing nitrates is an integral part of the Water Framework Directive 2000/60/EC [28]. Both the Water Framework Directive [28] and the Groundwater Directive 2006/118/EC [29] confirm

that nitrate concentrations must not exceed the trigger value of 50 mg L⁻¹, as laid down in the Drinking Water Directive 98/83/EC [30] and the Nitrate Council Directive [24]. Besides nitrate in groundwater, the Water Framework Directive [28] specifies environmental quality standards in surface water for certain substances or groups of substances (among them, VMPs are currently discussed) identified as a priority, on account of the substantial risk that they pose to or via the aquatic environment. RMM will be required if the environmental quality standard of a substance is exceeded.

RMM affecting animal husbandry should be in accordance with the provisions of the Animal Welfare Act [31] and the order on the keeping of production animals [32] or respective guidelines.

4. Proposed RMM for Use within the Authorization of VMP

When assessing the compiled RMMs according to the above described evaluation criteria and considering the legal boundaries given by German laws, a list of 19 reasonable and appropriate RMMs are proposed and shown in Table 2. This list resulted from excluding those RMMs that did not fulfil all of the above-mentioned criteria (Section 3.1), or as far as possible, RMMs were adapted in such a way that the criteria were generally fulfilled. For example, the criteria “addressing” was not considered in all compiled RMMs from existing VMPs (Section 2.1). Therefore, in all RMMs proposed in Table 2, the addressee, *i.e.*, the professional group that is in control of the specific constraint, was included. Some RMMs, whether compiled (Section 2.1) or derived from exposure models (Section 2.2), with analogous content, were combined by harmonizing and improving the wording in order to fulfil the criteria. For example, the existing precautions for disposal “should not enter surface waters” and “should not enter the environment” were combined (with others), resulting in the precaution for disposal D-01 (Table 2). Consequently, the RMMs shown in Table 2 are an aggregation of existing RMMs, with derived RMMs as shown above.

The list is divided into five categories that address the following precautions for VMPs: disposal, use in aquaculture, use in intensively reared animals, use in pasture animals and combined use in intensively reared and pasture animals.

Table 2. Catalogue of proposed appropriate and effective risk mitigation measures (RMMs), which may support applicants and competent authorities within the process of the authorization of veterinary medicinal products (VMPs).

Precautions for disposal	
D-01	The user (e.g., veterinarian or livestock owner) has to ensure that any unused product or waste materials derived from the product, such as empty containers, do not contaminate water courses, surface waters or other parts of the environment. Veterinary pharmaceutical products must not be disposed of via sewage, but should be disposed of preferentially via local return systems for hazardous waste. If disposed with household waste, it should be taken care that no misuse of these wastes could occur.
D-02	The user (e.g., veterinarian or livestock owner) has to ensure that any unused product or the rest of the dip do not contaminate water courses, surface waters or other parts of the environment. Dips must not be disposed of via sewage, but should be disposed of via local return systems for hazardous waste.

Table 2. Cont.

Precautions for use in aquacultures	
U-01	Constraint to the user (fish owner): Prior to the use of the product, a discharge certificate is required from the relevant authority for the release of this product into the aquatic environment.
U-02	Constraint to the user (fish owner): Use only if the flow rate of untreated waters allows for an x -fold dilution of the volume of treated water before discharge into surface waters. Where the appropriate dilution of treated water cannot be achieved, the farm must have a discharge process to limit the release of product into the environment to within the parameters described. This can be achieved by the use of holding tanks and ponds, discharge lagoons and biofilters to clean treated water. Where this applies, the user must monitor the discharge concentration to ensure that the parameters are not exceeded.
Precautions for use in intensively reared animals	
U-11	Constraint to the farmer: Before spreading slurry (manure) from treated animals, it has to be stored for at least x days/months.
U-12	Constraint to the farmer: Slurry (manure) from treated animals must not be spread on areas where run-off could occur (slope > 10%).
U-13	Constraint to the farmer: Slurry (manure) from treated animals must only be spread on arable land if it is x -fold diluted with slurry (manure) from untreated animals.
U-14	Constraint to the farmer: When spreading slurry (manure) from treated animals onto arable land, a safety margin of x meters to the water's edge has to be maintained.
U-15	Constraint to the farmer: When spreading slurry (manure) from treated animals onto arable land, the maximum nitrogen spreading limit must not exceed x kg N ha ⁻¹ yr ⁻¹ .
U-16	Constraint to the farmer: Slurry (manure) from treated animals must only be spread on arable land in x portions of the maximum nitrogen spreading limit with minimum time intervals of y days.
U-17	Constraint to the farmer: Slurry (manure) from treated animals must not be spread on soils with an organic C content < x %.
U-18	Constraint to the farmer: After spreading of slurry (manure) from treated animals, soil must be ploughed to a depth of at least x cm (>5 cm).
Precautions for use in pasture animals	
U-21	Constraint to the veterinarian/animal holder: Strategic treatment of stock is only allowed after the fly or dung beetle season in autumn or in early spring.
U-22	Constraint to the animal holder: Animals [animal group] from free-range husbandry must be kept indoor during treatment and x days following treatment.
U-23	Constraint to the animal holder: During treatment and x hours/days following treatment animals [animal group] must be kept away from watercourses.
U-24	Constraint to the animal holder: [Product] is toxic to dung organism (flies, beetles). Therefore, animals [animal group] must not be kept on the same pasture every season.
Precautions for use in intensively reared and pasture animals	
U-31	Constraint to the veterinarian/animal holder: Only treat affected animals [animal group] when required. For correct diagnosis and development of an appropriate treatment schedule, a veterinarian should be consulted. Fecal worm (worm egg) counts can be used as an indicator of whether treatment is needed or not.
U-32	Constraint to the user of the product: During the use of the teat dipping or spraying, dripping residues must be collected and disposed of separately (<i>cf.</i> special precautions for disposal, SmPC, Section 6.6).
U-33	Constraint to the farmer: Dirty water must only be spread with a maximum spreading rate of x L (<50,000) ha ⁻¹ onto arable land or pastures.

5. Evaluation of RMMs for HMPs

Although for HMPs refusal of the marketing authorization application due to environmental concerns is not foreseen, RMMs can also be applied [8,11] following an ERA. Within the authorization procedures of HMP, no RMM have been applied so far, except for specific precautions for the disposal of the unused medicinal product or used waste materials. An example is a special precaution for the disposal of the transdermal patch, EVRA[®], for female contraception. The used patch should be discarded using the protective sachet in which the unused patch is sealed. Furthermore, it is

advised that “used patches should not be flushed down the toilet nor placed in liquid waste disposal systems”. Similar precautions are applied for other medicinal transdermal patches containing narcotic substances, such as fentanyl.

For HMPs, besides the general precautionary measures contained in the guideline on environmental risk assessment [1], such as special precaution for disposal, no additional parameter was identified as a source for new RMMs.

The above-mentioned criteria (except of Criteria 6) for the evaluation of RMMs for VMPs principally do also apply for HMPs. However, the most important criterion for possible RMMs applied for HMPs is that the physicians’ freedom for selection of the most appropriate medical treatment is ensured, i.e., the measure must be compatible with the existing healthcare system. This is also reflected in the fact that within the marketing authorization of HMP, human health issues must not be weighed against environmental issues, whereas for VMP, the benefit for the target species has to be weighed against environmental risks within the authorization procedure.

Finally, within this research project, except for the existing precautions for disposal, no further reasonable measures could be developed for HMPs.

6. Discussion and Conclusions

In several SmPCs of authorized products, no RMM was applied. This is of specific interest, since according to the precautionary principle, it is recommended to include at least one of the proposed “precautions for disposal”, even if no unacceptable environmental risk is identified when conducting the ERA. This is also required for the background of the EU Water Framework Directive [28], which demands measures to prevent the deterioration of the quality of surface water bodies.

Within this study, only for VMPs, existing and new RMMs could be compiled and optimized, resulting in the catalogue presented in Table 2. For HMPs, except for the existing precautions for disposal, no further RMMs could be generated. This is caused by the diffuse exposure pathway of pharmaceuticals via sewage in contrast to the local exposure of VMPs via organic fertilizer, where RMMs can take effect. Moreover, physicians’ freedom for selection of the most appropriate medical treatment must be kept ensured for HMPs, and human health issues must not be weighed against environmental issues within the marketing authorization of HMPs.

In some exceptional cases the proposed RMMs for VMPs shown in Table 2 could not fulfil all the evaluation criteria, in particular the criteria of practicability and commensurability. Some of the proposed RMMs might not be applicable to small or medium sized farms, due to geographic conditions or the reduced availability of arable land. Furthermore, on farms with year-round free-range husbandry, the use of some RMMs related to the temporary indoor housing of animals might not be possible. Despite these deficits, which are probably confined to a relatively small number of users, it is expected that the implementation of the proposed RMMs will considerably reduce the exposure of the product in question to the environment. The general acceptability of the proposed RMMs is further supported by the fact that they are consistent with the current European and German legislation and in accordance with good agricultural practices.

An important issue is the product-specific authorization procedure of pharmaceuticals; this requirement assists the generation of independent ERAs for products containing the same active

ingredient(s) that, at the same time, show only minor or environmentally non-relevant modifications in the composition of the associated substances (formulation). A product-specific approach might provide some interesting insight in to the variability of the fate and effects data obtained under standardized test conditions; on the other hand, theoretically, this approach could lead to an acceptable risk for one product, but to an unacceptable risk for another product with the same active ingredient, whereupon the outcome is less caused by dissimilarities between formulations than by the common variability of test results. Consequently, this approach seems not to be justified to the user/farmer. As pointed out in a notice to applicants [33], the use of a monograph system would tackle this problem, avoiding repeatedly performing effect studies with the same active ingredient and the assessment based on different study results, leading to a more harmonized and equitable environmental risk assessment, resulting in the same RMMs for products with the same active ingredient.

Furthermore, the monograph system would foster the derivation of environmental quality standards for pharmaceuticals, which are required as part of the eco-pharmacovigilance system for the evaluation of the chemical monitoring results [9,10,34,35].

Whereas the violation of RMMs for pesticides has legal consequences, the non-compliance with RMMs for pharmaceuticals is not considered as an infringement of European or national law [23]. To improve the effectiveness of RMMs, it is proposed to establish appropriate legal instruments that can enforce compliance with RMMs for pharmaceuticals.

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Conflicts of Interest

The authors declare no conflict of interest.

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by the European Medicines Agency (EMA) in London. For more information about the different marketing authorisation procedures in the European Community please refer to EMA (<http://www.ema.europa.eu/ema/>).

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