EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2021
EMA/CVMP/ERA/173026/2021
Committee for Medicinal Products for Veterinary Use

# Concept paper on the development of a guideline on the environmental risk assessment of veterinary medicinal products intended to be used in aquaculture

| | |
|---|---|
| Agreed by ERAWP | June 2021 |
| Adopted by CVMP for release for consultation | 15 July 2021 |
| Start of public consultation | 23 July 2021 |
| End of consultation (deadline for comments) | 31 October 2021 |

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

| | |
|---|---|
| **Keywords** | **Aquaculture, environmental risk assessment, veterinary medicinal product, exposure assessment, guideline development** |

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# 1. Introduction

In the EU, according to current[1] and soon-to-be-applicable[2] legislation, every dossier submitted in support of a new application for a marketing authorisation for a veterinary medicinal product (VMP) needs to be accompanied by an environmental risk assessment (ERA) evaluating the risk of the product towards the environment. For pharmaceuticals, such an assessment is usually carried out in two phases according to VICH guidelines (GL) 6[3] and 38[4] as well as accompanying CVMP guidance[5]. The first phase thereby consists of an estimation of the product's exposure to the environment, which is then subsequently refined in phase II should the initial worst-case exposure exceed certain threshold limits.

While the available guidance documents (see above for details) provide detailed information on how to estimate the environmental exposure of VMPs intended for use in terrestrial animals, they do not provide comprehensive guidance on how to perform an ERA for VMPs intended for use in aquaculture facilities.

The lack of (clear) guidance on how to perform an ERA for aquaculture facilities (e.g. cages, net pens, raceways, ponds) may therefore result in varying ERA approaches being taken across the EU, which in turn may result in different ERA outcomes and the application of different risk mitigation measures.

In order to eliminate this disharmonisation, which has the potential to impact on the availability of VMPs needed in the aquaculture sector, and to provide clarity on the scientific approach to be taken in the assessment of relevant products, the ERAWP was tasked with developing guidance on the ERA of VMPs intended for use in aquaculture.

# 2. Problem statement

VICH GL 6 (phase I) and VICH GL 38 (phase II) outlining the ERA procedure for VMPs do not provide detailed guidance on the assessment of veterinary medicinal products intended to be used in aquaculture, nor clearly define protection goals of the assessment.

In phase I of the ERA for VMPs a 100% release to the environment is normally assumed, irrespective of the type of production facility, treated species, route of administration or behaviour of the molecule after administration. Following the principles of the total residue approach, the environmental introduction concentration (EIC) is equal to the recommended dose. If the EIC is (i) higher than a threshold value of 1 µg/l; or/and (ii) if the VMP is an ecto- and/or endoparasiticide; or/and (iii) the aquatic species are reared in a non-confined facility, the assessment of environmental risk should proceed to phase II. It should be noted that no predicted environmental concentration (PEC) calculation is needed in phase I.

Phase II of the ERA for VMPs does not provide any detailed recommendations on the calculation of the initial surface water PEC ($PEC_{sw\text{-}initial}$), nor any suggestions on any further refinement of this value. Consequently, the evaluation of the ratio between the exposure and potential adverse environmental effects (risk quotient, RQ) of VMPs intended to be used in aquaculture is subject to disharmonisation that could potentially lead to differing risk characterisations applied within the EU and to an unfair treatment of applicants.

In addition, a phase II tier A assessment according to VICH GL 38 only requires a subsequent tier B ERA of the VMP in question if the (refined) RQ, derived from the acute ecotoxicity tests and the $PEC_{sw\text{-}initial}$, is ≥ 1. This immediately excludes some VMPs from a more detailed assessment even though they may be biologically active at concentrations far lower than those needed to cause acute toxicity. This decision point should be amended to consider other possible effects on non-target organisms in the

environment. Furthermore, if a tier B assessment is required, sub-lethal NOEC values from chronic studies need to be determined based on the corresponding taxonomic group that had the highest RQ in the tier A assessment. However, these latter tests are poorly defined in the VICH GLs, which only specify that regulatory guidance needs to be sought regarding the appropriate test.

There is also a strategic need to have clear guidance on the ERA for VMPs to be used in aquaculture. In this regard, the European Commission's "Strategic Approach to Pharmaceuticals in the Environment"[6] contains specific actions aiming to "[c]onsider developing guidance on the environmental risk assessment of medicinal products for use in aquaculture […]". Furthermore, EMA's "Regulatory Science to 2025"[7] strategic reflection also recommends the development of "[…] additional guidance on the ERA of active substances used in aquaculture […]" in order to achieve the general goal of improving the scientific quality of evaluations. In addition, Article 114(3) of Regulation (EU) 2019/6 establishes that substances included in VMPs intended for use in terrestrial food-producing animals can only be used "off-label" in aquaculture in case they are included in a specific list, which is to be developed by the Commission within five years of the coming into force use of said regulation. One of the issues to be thereby taken into account in the frame of the creation of such a list is the risks for the environment arising from the treatment of the aquatic species with the substance in question, so suitable guidance will also be needed for that exercise.

# 3. Discussion

The guideline on the assessment of VMPs intended to be used in aquaculture will address the following items:

- Protection goals of the environmental risk assessment.
- Specific formulas or models to calculate the initial PEC to be used in phase II for confined and non-confined aquaculture.
- Specific formulas or models to refine the initial PEC when a risk is identified.
- Specific models for the refinement of higher tier assessments in phase II.
- A scenario to calculate the exposure of agricultural soils fertilised with fish sludge.
- A detailed list of the standard fate, behaviour and effect studies that should be considered for the ERA of each aquaculture system (i.e., marine or freshwater aquaculture).
- A detailed list of effect studies that should be considered for substances with a specific mode of action (e.g., parasiticides or antimicrobials).
- A discussion on the use of substances with potential persistent, bioaccumulative and toxic (PBT) properties.
- A discussion on possible risk mitigation measures (RMMs).

# 4. Recommendation

The Committee for Medicinal Products for Veterinary Use recommends drafting a "Guideline on the environmental risk assessment of veterinary medicinal products intended to be used in aquaculture" considering the issues identified above.

Based on potential exposure, the protection goals of the ERA will be identified. The scale of protection as well as different communities will be set for different environmental compartments.

In phase II assessments, the estimation of exposure will be based on specific formulas or models to calculate the initial PEC and to refine the initial PEC when a risk is identified. The existing calculations, environmental compartments and species-related default values will be re-evaluated.

Site-specific exposure models for higher-tier refinement will be suggested if the realistic worst-case estimation in phase II tier A identifies a risk.

The "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- Corr.1) indicates slurry application and the direct and indirect entry into surface waters as the predominant routes of environmental exposure from confined and non-confined fish farms. Consequently, a scenario to calculate the exposure of agricultural soils fertilised with fish sludge will be developed.

The assessment of the environmental distribution and the effect of the VMPs in aquaculture will be based on standard fate, behaviour and effect studies. The list of studies that should be considered for the ERA of each aquaculture system (i.e. marine or freshwater aquaculture) proposed in VICH GL38 will be carefully reviewed and, if needed, consideration will be given to updating the list.

The list of effect studies relevant for substances used in aquaculture production will be reviewed. The option of a tailored risk assessment will be addressed in case hazards are inherently associated with certain classes of substances such as parasiticides or antimicrobials.

A hazard assessment of PBT properties of VMPs is undertaken according to existing guidelines (EMA/CVMP/ERA/418282/2005 and EMA/CVMP/ERA/52740/2012). The guideline proposed in the current concept paper will address data and protocols related to VMPs with PBT properties intended to be used in aquaculture.

Possible RMMs will be discussed for each of the production methods (marine production in cages, freshwater raceway and pond production).

# 5. Proposed timetable

Release for consultation of the concept paper: July to October 2021.

Proposed date for release for consultation of the draft guideline: October 2023.

Deadline for comments: April 2024.

Expected date for adoption by CVMP: October 2024.

# 6. Resource requirements for preparation

The CVMP Environmental Risk Assessment Working Party to prepare the guideline. Two rapporteurs and 4 members of the drafting group have been appointed. Discussion of the draft guideline is expected to take place during at least 6 working party meetings and at least 6 drafting group meetings. If considered necessary, a workshop involving various stakeholders and experts will be organised in the first year of the drafting of the guideline.

# 7. Impact assessment (anticipated)

The guideline will provide clear guidance on how to perform an ERA for VMPs intended to be used in aquaculture. The impact of the guideline for industry, regulatory authorities and other interested parties is therefore considered to be high, as it will reduce the current regulatory uncertainty and

disharmonisation while simultaneously ensuring an increase of public and animal health/welfare as well as environmental protection.

# 8. Interested parties

Pharmaceutical industry, (national) competent regulatory authorities (including environmental protection and aquaculture/fisheries agencies), aquaculture industry, VICH, (environmental) non-governmental organisations.

# 9. References to literature, guidelines, etc.


[1] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. OJ L 311, 28.11.2001, p. 1–66.

[2] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC. OJ L 4, 7.1.2019, p. 43–167.

[3] VICH Topic GL6 (ecotoxicity phase I): Guideline on environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL).

[4] VICH GL38 (ecotoxicity phase II): Environmental impact assessment for veterinary medicinal products (VMPs) phase II (CVMP/VICH/790/03-FINAL).

[5] 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- Corr.).

[6] Communication from the Commission to the European Parliament, the Council, and the European Economic and Social Committee: European Union Strategic Approach to Pharmaceuticals in the Environment (COM/2019/128 final).

[7] EMA Regulatory Science to 2025 — Strategic reflection (EMA/110706/2020).