16 April 2026
EMA/CVMP/724/2026
Committee for Veterinary Medicinal Products

Guidance under Article 141(1)(f) of Regulation (EU) 2019/6 on veterinary medicinal products in relation to Articles 107(6) and 114(3)

Introduction

In a letter dated 2 December 2025, the European Commission requested EMA's Committee for Veterinary Medicinal Products (CVMP) to provide guidance pursuant to Article 141(1)(f) of Regulation (EU) 2019/6[1] on scientific issues in relation to Articles 107(6) and 114(3).

The scientific advice under Article 107(6)[2] and the scientific advice under Article 114(3)[3] were based on different sets of criteria established in Regulation (EU) 2019/6. In order to ensure coherence between the respective implementing acts, the Commission asked the CVMP to respond to some questions on nine antimicrobial substances by 30 April 2026. These questions relate to the mitigation of antimicrobial resistance (AMR) risk by the proposed set of conditions.

It should be noted that both questions concerning enrofloxacin, flumequine, oxalinic acid, difloxacin, cefaperazone, cefquinome and ceftiofur posed by the European Commission have been understood to specifically ask if the proposed or recommended conditions can satisfactorily mitigate the risks to animal and public health from AMR, as identified in the scientific advice under Article 107(6). The CVMP did not interpret the questions as a request to balance the risks of AMR against the needs of the aquaculture sector. The availability of treatment options for food-producing aquatic species and the associated impact on animal health have not been further considered as part of this guidance (although they have been previously considered in the two previous scientific advices), as the CVMP finds that they were outside of the scope of the questions asked by the Commission.

To prepare the guidance, the CVMP appointed two of its members as rapporteur and co-rapporteur, and noted the participation of three members or chair of the expert groups who prepared both scientific advice mentioned above.

[1] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, available from: https://eur-lex.europa.eu/eli/reg/2019/6/oj/eng
[2] Scientific advice under Article 107(6) of Regulation (EU) 2019/6 for the establishment of a list of antimicrobials which shall not be used in accordance with Articles 112, 113 and 114 of the same Regulation or which shall only be used in accordance with these articles subject to certain conditions (EMA/CVMP/151584/2021), available from: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/vet_reg_cascade_list_report_en.pdf
[3] Scientific advice under Article 114(3) of Regulation (EU) 2019/6 on veterinary medicinal products - List of substances used in veterinary medicinal products authorised in the Union for use in food-producing terrestrial animal species or substances contained in medicinal products for human use authorised in the Union, which may be used in food-producing aquatic species in accordance with Article 114(1) (EMA/CVMP/29892/2024), available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/scientific-advice-under-article-1143-regulation-eu-2019-6-veterinary-medicinal-products-list-substances-used-veterinary-medicinal-products-authorised-union-use-food-producing-terrestrial-animal_en.pdf

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A draft of this guidance was submitted to the CVMP on 6 March 2026 for discussion.

The CVMP adopted the guidance on 16 April 2026.

1. Terms of reference and scope

1.1. Request from the European Commission

The European Commission is seeking the guidance of the Committee for Veterinary Medicinal Products (CVMP) pursuant to Article 141(1)(f) of Regulation (EU) 2019/6.

In accordance with Article 114(3) of Regulation (EU) 2019/6, the Commission is to adopt an implementing act listing substances that may be used in food-producing aquatic species in accordance with Article 114(1). The Commission also intends to extend the scope of Commission Implementing Regulation (EU) 2024/1973[4] to food-producing aquatic species.

The Agency's scientific advice under Article 107(6)[5] included recommendations concerning food-producing aquatic species. The Agency's scientific advice under Article 114(3)[6] contains recommendations for listing several antimicrobials. Those two sets of recommendations are based on different sets of criteria established in Regulation (EU) 2019/6.

In this context, the Commission identified nine antimicrobial substances for which CVMP's guidance would be needed. In view of the Agency's recommendations and to ensure coherence between the implementing acts referred to above, the Commission is considering a set of possible conditions for each of those substances. Given the necessity for science-based decisions, the Commission therefore seeks CVMP's feedback on the questions below.

Regulation (EU) 2019/6 requires that the list of substances allowed for use in food-producing aquatic species under Article 114(1) be established by means of implementing acts adopted by January 2027. To ensure compliance with that legal deadline, the Commission expects the replies to the questions below no later than 30 April 2026.

<table>
<tr><td colspan="2">SUBSTANCES [assessed in scientific advice under Article 114(3)]: enrofloxacin, flumequine, oxolinic acid

GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)</td></tr>
<tr><td colspan="2">ENROFLOXACIN, FLUMEQUINE and OXOLINIC ACID are widely authorised, e.g:
• In fish, for group administration via feed
• In cattle, pigs and chicken, for group administration via water.</td></tr>
<tr><td>EMA recommendation under Article 114(3)</td><td>Relevant EMA recommendations under Article 107(6)</td></tr>
</table>

[4] Commission Implementing Regulation (EU) 2024/1973 of 18 July 2024 establishing a list of antimicrobials which shall not be used in accordance with Articles 112 and 113 of Regulation (EU) 2019/6 of the European Parliament and of the Council or which shall only be used in accordance with those Articles subject to certain conditions, available from: http://data.europa.eu/eli/reg_impl/2024/1973/oj

[5] Scientific advice under Article 107(6) of Regulation (EU) 2019/6 for the establishment of a list of antimicrobials which shall not be used in accordance with Articles 112, 113 and 114 of the same Regulation or which shall only be used in accordance with these articles subject to certain conditions (EMA/CVMP/151584/2021), available from: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/vet_reg_cascade_list_report_en.pdf

[6] Scientific advice under Article 114(3) of Regulation (EU) 2019/6 on veterinary medicinal products - List of substances used in veterinary medicinal products authorised in the Union for use in food-producing terrestrial animal species or substances contained in medicinal products for human use authorised in the Union, which may be used in food-producing aquatic species in accordance with Article 114(1) (EMA/CVMP/29892/2024), available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/scientific-advice-under-article-1143-regulation-eu-2019-6-veterinary-medicinal-products-list-substances-used-veterinary-medicinal-products-authorised-union-use-food-producing-terrestrial-animal_en.pdf

Enrofloxacin, flumequine and oxolinic acid to be included in the list with the following condition: • B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.	• For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible. • When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product should be administered to individual animals, only. • Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. Implementing act under Article 114(3):

- enrofloxacin, flumequine, oxolinic acid to be included in the list with the proposed condition B (blanket).

2. Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:

- not to restrict the use of enrofloxacin, flumequine, oxolinic acid to individual animals only.
- to impose condition B (blanket) to the use of extemporaneous VMPs containing the three substances.

Rationale

- The VMPs authorised for fish are already being used in groups by virtue of their marketing authorisations.
- The scientific advice under Article 107(6) does not recommend restricting the use of the three substances to individual food-producing aquatic animals except for the use cases below: a route of administration different from the one covered by the terms of the marketing authorisation of VMPs, medicinal products for human use, extemporaneous products.
- The VMPs authorised for food-producing aquatic animals are outside the scope of Article 114(3) and are to be used outside the terms of their marketing authorisations in groups of food-producing aquatic animals, without any condition mitigating the environmental exposure.
- The VMPs authorised for food-producing terrestrial species or medicinal products for human use will be used in food-producing aquatic animals only where the VMPs authorised for such animals are not available.
- The scientific advice under Article 114(3) concludes that if the three substances cannot be used in groups of animals the impact on animal health is considered high.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising the exposure. To mitigate risks and for consistency in the use of each substance, condition B (blanket) should also apply to extemporaneous VMPs containing the three substances.

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of enrofloxacin, flumequine and oxolinic acid under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?

SUBSTANCES [assessed in scientific advice under Article 114(3)]: difloxacin

GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)

DIFLOXACIN: Authorised for group administration in water in chicken and turkeys

EMA recommendation under Article 114(3)

Difloxacin to be included in the list with the following conditions:

- B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.

Relevant EMA recommendations under Article 107(6)

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product should be administered to individual animals, only.
- Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. Implementing act under Article 114(3):

- difloxacin to be included in the list with the proposed condition B (blanket).

2. Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:

- not to restrict the use of difloxacin to individual animals only.
- to impose condition B (blanket) to the use of extemporaneous VMPs containing difloxacin.

Rationale

- Difloxacin is authorised for group administration in water in food-producing terrestrial species (chickens and turkeys), only turkeys considered limited market.
- In accordance with Commission Implementing Regulation (EU) 2024/1973, the difloxacin-containing VMP can also be administered via water to groups of any other food-producing terrestrial animal species under Article 113(1)(a).
- The scientific advice under Article 114(3) concludes that difloxacin is needed to treat or prevent infectious diseases, for which there is lack of availability of other treatments or measures in food-producing aquatic species, and if difloxacin cannot be used in groups of animals the impact on animal health is considered high.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising environmental exposure to microbiologically active effluent. To mitigate risks and for consistency in the use of difloxacin, condition B (blanket) should also apply to extemporaneous VMPs containing difloxacin.
- The total biomass of finfish in the EU represents 0.52% of the total biomass of food-producing animals, while chicken represent 18.64% of the total biomass of food-producing animals in the EU.

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of difloxacin under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?

SUBSTANCES [assessed in scientific advice under Article 114(3)]: danofloxacin and marbofloxacin
GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)

DANOFLOXACIN: authorised for injection in cattle and pigs
MARBOFLOXACIN: Authorised for injection in cattle and in pigs

EMA recommendation under Article 114(3)	**Relevant EMA recommendations under Article 107(6)**
Danofloxacin and marbofloxacin to be included in the list with the following conditions: • B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.	• For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible. • When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product

	should be administered to individual animals, only. Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. **Implementing act under Article 114(3):**
   - danofloxacin and marbofloxacin to be included in the list with:
     - condition B (blanket) and
     - condition S (use restricted to individual animals only).
2. **Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:**
   - the restrictions to use in individual animals only, which, by virtue of Commission Implementing Regulation (EU) 2024/1973, are currently applicable to the use of *Quinolones (including Fluoroquinolones*) under Articles 112 and 113 of Regulation (EU) 2019/6, to apply also to the uses of danofloxacin and marbofloxacin under Article 114.

Rationale

- Danofloxacin and marbofloxacin are authorised for individual administration only.
- It is understood that the extent of additional exposure (and associated AMR risks) due to group administration under Article 114(1)(b) and (c) can be relatively big. Therefore, the restrictions to use in individual animals only, which are currently applicable to *Quinolones (including Fluoroquinolones)*, should apply also to the uses of danofloxacin and marbofloxacin under Article 114.
- The scientific advice under Article 107(6) when assessing AMR risks related to the use in aquaculture seems to have considered mainly 'open' aquaculture systems.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising the exposure.
- It is understood that the treatment of individual food-producing aquatic animals will likely take place in 'closed' setups where the effluent can be confined and controlled and consequently, environmental exposure to microbiologically active effluent is likely to be limited.
- The scientific advice under Article 114(3) concludes that danofloxacin and marbofloxacin are needed to treat or prevent infectious diseases, for which there is lack of availability of other treatments or measures in food-producing aquatic species, and if danofloxacin and marbofloxacin cannot be used in groups of animals the impact on animal health is considered high.

Questions for the CVMP

1. If other quinolones (difloxacin, enrofloxacin, flumequine, oxolinic acid) were to be included in the list under Article 114(3) without restriction to be used only in individual food-producing aquatic animals, would you consider that restricting the use of marbofloxacin and danofloxacin under Article 114(1)(b) and (c) only to individual food-producing aquatic animals no longer has a high impact on animal health?
2. In the negative, what would be recommended?

SUBSTANCE [assessed in scientific advice under Article 114(3)]: cefoperazone, cefquinome, ceftiofur

GROUP [assessed in scientific advice under Article 107(6)]: 3rd- & 4th-generation cephalosporins

EMA recommendations under Article 114(3)	**Relevant EMA recommendation under Article 107(6)**
Cefoperazone, cefquinome, ceftiofur to be included in the list with the following conditions: • B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible, • S – use restricted to individual animals only, • C – not to be used in combination with BLI	• 3rd- and 4th-generation cephalosporins not to be used in food-producing aquaculture.

Proposed set of conditions

1. **Implementing act under Article 114(3):**
   - cefoperazone, cefquinome, ceftiofur to be included in the list with:
     - condition B (blanket) and
     - condition S (use restricted to individual animals only).
2. **Amendment of Commission Implementing Regulation (EU) 2024/1973 to expand the scope to Article 114:**
   - 3rd- and 4th-generation cephalosporins to be allowed for use only in individual food-producing aquatic animals.
   - to specify that the conditions in Commission Implementing Regulation (EU) 2024/1973 are without prejudice to the conditions laid down in the implementing act under Article 114(3).
   - to explain in the recitals that the conditions imposed by the various regulations, such as Commission Implementing Regulation (EU) 2022/1255, should be seen as cumulative/complementary.
3. **Commission Implementing Regulation (EU) 2022/1255 already prohibits the use in all animals of cefoperazone, cefquinome, ceftiofur in combination with beta-lactamase inhibitors.**

Rationale

- For food-producing terrestrial species, cefoperazone, cefquinome and ceftiofur are authorised for individual use only.
- The scientific advice under Article 114(3) recommends allowing use in individual food-producing aquatic animals only.
- The scientific advice under Article 107(6), when assessing AMR risks related to the use in aquaculture, seems to have considered mainly 'open' aquaculture systems.

- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising the exposure.
- It is understood that the treatment of individual food-producing aquatic animals will likely take place in 'closed' setups where the effluent can be confined and controlled and consequently, environmental exposure to microbiologically active effluent is likely to be limited.
- The scientific advice under Article 114(3) concludes that cefoperazone, cefquinome, ceftiofur are needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of cefoperazone, cefquinome and ceftiofur under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?

1.2. Clarifications

The previous scientific advice provided under **Article 114(3)** took into account the following criteria:

(a) risks to the environment if the food-producing aquatic species are treated with those substances. [In the case of antimicrobials, the development of resistance as a result of exposure of the environment and the related risks for animal and public health were considered to be outside the scope of criterion (a) and instead were addressed in a separate scientific advice under Article 107(6)];

(b) impact on animal and public health if the food-producing aquatic species affected cannot receive an antimicrobial listed in accordance with Article 107(6);

(c) availability or lack of availability of other medicinal products, treatments or measures for prevention or treatment of diseases or certain indications in food-producing aquatic species.

The previous scientific advice under **Article 107(6)** took into account the following criteria:

(a) risks to animal or public health if the antimicrobial is used in accordance with Articles 112, 113 and 114;

(b) risk for animal or public health in case of development of antimicrobial resistance;

(c) availability of other treatments for animals;

(d) availability of other antimicrobial treatments for humans;

(e) impact on aquaculture and farming if the animal affected by the condition receives no treatment.

2. Responses from the CVMP

2.1. Enrofloxacin, flumequine and oxolinic acid

The CVMP is asked whether the proposed set of conditions satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of enrofloxacin, flumequine and oxolinic acid under Article 114(1)(b) and (c), and if not, what conditions would be recommended?

Within the context of the scientific advice procedure under Article 114(3), enrofloxacin, flumequine and oxolinic acid were identified by the aquaculture sector as important for the treatment of food-producing aquatic species.

Conclusions arising from the scientific advice under Article 107(6)

The following conclusions were reached within the context of the previous scientific advice under Article 107(6) provided by the CVMP in June 2023 for enrofloxacin, flumequine and oxolinic acid as it relates to use under Article 114:

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, the product should be administered to individual animals, only.

Conclusions arising from the scientific advice under Article 114(3)

The following conclusions were reached within the context of the previous scientific advice under Article 114(3) provided by the CVMP in May 2025 for enrofloxacin, flumequine and oxolinic acid:

- If the substances cannot be used in animals other than individual animals, the impact on animal health is considered high.
- Other antibacterials are authorised for use in food-producing aquatic species. However, the alternative antibiotics do not necessarily pose a lesser risk to the environment. Enrofloxacin has a history of well-established use in food-producing aquatic species as a last resort. A spectrum of substances (including fluoroquinolones) for treating bacterial infections are needed to be able to choose substance according to situation.
- The substances are expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available. If the substances can be used by multiple application methods, the method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect must be selected.
- When possible, any treatment shall take place in a closed system with:

  a) removal or inactivation of the substances in used treatment water or solid waste before discharge into the environment

b) if (a) is not possible, contaminated water should be released into a recognised wastewater treatment system

c) if neither (a) nor (b) are possible, dilution of contaminated water so that the substances are present at concentration levels lower than 1 µg/L is required before discharge in the environment.

Recommended conditions of use and risk mitigation measure codes: enrofloxacin (B); flumequine (B); oxolinic acid (B).

[B: expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available; to be used by the application method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect; when possible, any treatment shall take place in a closed system (see above)].

CVMP view

According to the scientific advice provided by CVMP under Article 114(3), enrofloxacin, flumequine and oxolinic acid were identified by the aquaculture sector as important for the treatment of food-producing aquatic species.

In their request for guidance, the Commission proposes that the implementing act under Article 114(3) includes the condition B (blanket) as reflected by the risk mitigation measure code B in the scientific advice under Article 114(3) for enrofloxacin, flumequine and oxolinic acid. That is, use is expected to be harmful to the aquatic environment and therefore such products should only be used if other, less environmentally harmful treatment options are not available. This approach is in line with the previous scientific advice provided by the CVMP and the inclusion of this condition is therefore supported.

The Commission also proposes the following when including in the scope of Commission Implementing Regulation (EU) 2024/1973 food-producing aquatic species (Article 114 of Regulation 2019/6), for those animal species :

- not to restrict the use of enrofloxacin, flumequine, oxolinic acid to individual animals only;
- to impose condition B (blanket) to the use of extemporaneously prepared VMPs containing the three substances.

The rationale set out by the Commission for such an approach is based on the fact that currently authorised VMPs containing these active substances are authorised for use in groups of animals (cattle, pigs, chickens) when administered via the drinking water and for group administration to fish when administered via medicated feed. It is highlighted that the scientific advice provided by CVMP under Article 107(6) only proposed restricting use to individual animals in specific circumstances (proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product) and the scientific advice provided under Article 114(3) concluded that if the substances cannot be used in animals other than individual animals, the impact on animal health is considered high.

The Commission suggests that by implementing condition B (blanket), it is understood that this would not only mitigate against environmental risks but also against AMR risks by minimising exposure.

With reference to the rationales set out in the two previous scientific advices (and noting the different criteria upon which each was based), the CVMP accepts that the implementation of condition B (blanket) mitigates not only environmental risks but is also expected to reduce the AMR risks by minimising exposure. Whilst it is agreed that such a risk mitigation measure would be expected to

minimise exposure to the aquatic environment, following use of the substances in aquaculture and in particular, assuming that the advice is followed that any treatment shall take place in a closed system when possible, the environment is only one source of exposure to antimicrobial resistance. AMR may also result from exposure to the active substances within treated animals, particularly under group treatment conditions, and it is unknown to what extent this source of risk is mitigated by environmental measures alone. It can be accepted that in the scientific advice provided under Article 107(6), the CVMP also considered (under criteria (a) and (b)) risk to animal or public health if the antimicrobial is used in accordance with Article 114 and the risk for animal or public health in case of development of AMR.

As indicated above, some risk mitigation measures to limit AMR were included in the previous scientific advice under Article 107(6) for use of (fluoro)quinolones in food-producing aquaculture animals. These include restricting the administration to individual animals only when the proposed route of administration is outside the terms of the SPC, or when using a human medicinal product or an extemporaneously prepared product.

From an environmental perspective, implementing condition B (blanket) for these three active substances is expected to adequately address the risk to the environment and does not appear to conflict with the previous scientific advice provided under Article 107(6).

Concerning the Commission's proposal not to restrict the use of enrofloxacin, flumequine and oxolinic acid to individual animals only, this is not consistent with the previous scientific advice provided by CVMP under Article 107(6), which advised that when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, the product should be administered to individual animals only. That scientific advice stated that there is little or no evidence supporting the efficacy or need for alternative routes of administration in relation to (fluoro)quinolones in farmed animals. Therefore, although the impact on farming/aquaculture of restriction to individual animal use cannot be foreseen, it is not expected to be significant.

Whilst it is acknowledged that enrofloxacin, flumequine and oxolinic acid are all currently authorised within the EU as VMPs for administration in medicated water to groups of animals (cattle, pigs, chickens) and in medicated feed to fish, there is no scientific evidence that specific risk mitigation measures for AMR could be imposed to justify a proposal not to restrict the use to individual animals when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product. Furthermore, there are no reasons why the risk of AMR development would differ in food-producing aquatic species compared to other species for which similar restrictions are currently included for (fluoro)quinolones in Commission Implementing Regulation (EU) 2024/1973. Although the Commission asks that if in the negative, what conditions would be recommended, the CVMP considers that in light of the previous scientific advice provided under Art 107(6), the conditions to adequately mitigate the risk of AMR arising from the use of this antimicrobial class in aquaculture, have already been identified in the scientific advice under Article 107(6).

Concerning the proposal to impose condition B (blanket) to the use of extemporaneously prepared VMPs containing any of the three substances, it is understood that this is made on the grounds that Article 114.1 (b) and (c) foresee the use of veterinary medicinal products or human medicinal products, respectively, that include substances to be included in the list to be established under Article 114.3, whereas the use of an extemporaneously prepared product in accordance with Article 114.1 (d) does not make reference to that list.

Given that environmental exposure and therefore risk of AMR from the environment may occur irrespective of whether a veterinary medicinal product, human medicinal product or an

extemporaneously prepared product containing any of the concerned substances is administered to food-producing aquatic species, the CVMP agrees with the Commission's proposal to amend Regulation (EU) 2024/1973 to impose condition B (blanket) for extemporaneously prepared veterinary medicinal products that include enrofloxacin, flumequine or oxolinic acid as active substance.

In conclusion, the set of conditions as proposed by the Commission are not accepted as satisfactorily mitigating the risks to animal or public health from AMR associated with the use of enrofloxacin, flumequine and oxolinic acid under Article 114(1)(b) and (c), when taking into consideration the conditions to be included in Commission Implementing Regulation (EU) 2024/1973, arising from the scientific advice previously provided by the CVMP under Article 107(6). Implementing condition B (blanket) for these three active substances is expected to adequately address the risk to the environment. However, the proposal not to restrict the use to individual animals when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, is not considered to satisfactorily mitigate the risks to animal or public health from AMR associated with the use of enrofloxacin, flumequine and oxolinic acid.

2.2. Difloxacin

The CVMP is asked whether the proposed set of conditions satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of difloxacin under Article 114(1)(b) and (c), and if not, what conditions would be recommended?

Conclusions arising from the scientific advice under Article 107(6)

The following conclusions were reached within the context of the previous scientific advice under Article 107(6) provided by the CVMP in June 2023 for difloxacin as it relates to use under Article 114:

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, the product should be administered to individual animals, only.

Conclusions arising from the scientific advice under Article 114(3)

The following conclusions were reached within the context of the previous scientific advice under Article 114(3) provided by the CVMP in May 2025 for difloxacin:

- If the substance cannot be used in animals other than individual animals, the impact on animal health is considered high.
- There is only a limited number of antibacterials authorised in food-producing aquatic species. There is a need for several antibacterial substances in case the more commonly used substances are unavailable, and to be able to choose the substance according to situation. The substance is needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species.

- The substance is expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available. If the substance can be used by multiple application methods, the method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect must be selected.
- When possible, any treatment shall take place in a closed system with:

  a) removal or inactivation of the substance in used treatment water or solid waste before discharge into the environment

  b) if (a) is not possible, contaminated water should be released into a recognised wastewater treatment system

  c) if neither (a) nor (b) are possible, dilution of contaminated water so that the substance is present at concentration levels lower than 1µg/L is required before discharge in the environment.

Recommended conditions of use and risk mitigation measure codes: Difloxacin (B).

[B: expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available; to be used by the application method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect; when possible, any treatment shall take place in a closed system (see above)].

CVMP view

According to the scientific advice provided by CVMP under Article 114(3), difloxacin was not identified by the aquaculture sector as important for the treatment of food-producing aquatic species.

In their request for guidance, the Commission proposes that the implementing act under Article 114(3) includes the condition B (blanket) as reflected by the risk mitigation measure code B in the scientific advice under Article 114(3) for difloxacin. That is, use is expected to be harmful to the aquatic environment and therefore such products should only be used if other, less environmentally harmful treatment options are not available. This approach is in line with the previous scientific advice provided by the CVMP and the inclusion of this condition is therefore supported.

The Commission also proposes the following: when including in the scope of Commission Implementing Regulation (EU) 2024/1973 food-producing aquatic species (Article 114 of Regulation 2019/6), for those animal species:

- not to restrict the use of difloxacin to individual animals only;
- to impose condition B (blanket) to the use of extemporaneously prepared VMPs containing difloxacin.

The rationale set out by the Commission for such an approach is based on the fact that currently authorised VMPs containing difloxacin are indicated for administration in water to food-producing terrestrial species (chickens and turkeys), difloxacin can be administered in drinking water (same route of administration) to groups of other food-producing terrestrial species and the scientific advice provided under Article 114(3) concluded that difloxacin is needed to treat or prevent infectious diseases, for which there is lack of availability of other treatments or measures in food-producing aquatic species. Further, if difloxacin cannot be used in groups of animals the impact on animal health is considered high.

The Commission suggests that by implementing condition B (blanket), it is understood that this would not only mitigate against environmental risks but also against AMR risks by minimising exposure to microbiologically active effluent. It is also highlighted that the total biomass of finfish in the EU represents 0.52% of the total biomass of food-producing animals, whilst chickens represent 18.64%.

With reference to the rationales set out in the two previous scientific advices (and noting the different criteria upon which each was based), the CVMP accepts that the implementation of condition B (blanket) mitigates not only environmental risks but is also expected to reduce the AMR risks by minimising exposure. Whilst it is agreed that such a risk mitigation measure would be expected to minimise exposure to the aquatic environment, following use of the substance in aquaculture and in particular, assuming that the advice is followed that any treatment shall take place in a closed system when possible, the environment is only one source of exposure to antimicrobial resistance. AMR may also result from exposure to the active substances within treated animals, particularly under group treatment conditions, and it is unknown to what extent this source of risk is mitigated by environmental measures alone. It can be accepted that in the scientific advice provided under Article 107(6), the CVMP also considered (under criteria (a) and (b)) risk to animal or public health if the antimicrobial is used in accordance with Article 114 and the risk for animal or public health in case of development of AMR. As indicated above, some risk mitigation measures to limit AMR were included in the previous scientific advice under Article 107(6) for use of (fluoro)quinolones in food-producing aquaculture animals. These include restricting the administration to individual animals only when the proposed route of administration is outside the terms of the SPC, or when using a human medicinal product or an extemporaneously prepared product.

From an environmental perspective, implementing condition B (blanket) for difloxacin is expected to adequately address the risk to the environment and does not appear to conflict with the previous scientific advice provided under Article 107(6).

Concerning the Commission's proposal not to restrict the use of difloxacin to individual animals only, this is not consistent with the previous scientific advice provided by CVMP under Article 107(6) which advised that when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, the product should be administered to individual animals only. That scientific advice stated that there is little or no evidence supporting the efficacy or need for alternative routes of administration in relation to (fluoro)quinolones in farmed animals. Therefore, although the impact on farming/aquaculture of restriction to individual animal use cannot be foreseen, it is not expected to be significant.

Whilst it is acknowledged that difloxacin is currently authorised in VMPs for administration in water to groups of animals (chickens and turkeys) and in accordance with Article 113(1)(a) may be administered via water to other food-producing animals at the group level, there is no scientific evidence that specific risk mitigation measures for AMR could be imposed to justify a proposal not to restrict the use to individual animals, when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product. Furthermore, there are no reasons why the risk of AMR development would differ in food-producing aquatic species compared to other species for which similar restrictions are currently included for (fluoro)quinolones in Commission Implementing Regulation (EU) 2024/1973. Although the Commission asks that if in the negative, what conditions would be recommended, the CVMP considers that in light of the previous scientific advice provided under Art 107(6), the conditions to adequately mitigate the risk of AMR arising from the use of this antimicrobial class in aquaculture, have already been identified in the scientific advice under Article 107(6).

Concerning the proposal to impose condition B (blanket) to the use of extemporaneously prepared VMPs containing difloxacin, it is understood that this is made on the grounds that Article 114.1 (b) and

(c) foresee the use of veterinary medicinal products or human medicinal products, respectively, that include substances to be included in the list to be established under Article 114.3, whereas the use of an extemporaneously prepared product in accordance with Article 114.1 (d) does not make reference to that list.

Given that environmental exposure and therefore risk of AMR from the environment may occur irrespective of whether a veterinary medicinal product, human medicinal product or an extemporaneously prepared product containing difloxacin is administered to food-producing aquatic species, the CVMP agrees with the Commission's proposal to amend Regulation (EU) 2024/1973 to impose condition B (blanket) for extemporaneously prepared veterinary medicinal products that include difloxacin as active substance.

In conclusion, the set of conditions as proposed by the Commission are not accepted as satisfactorily mitigating the risks to animal or public health from AMR associated with the use of difloxacin under Article 114(1)(b) and (c), when taking into consideration the conditions to be included in Commission Implementing Regulation (EU) 2024/1973, arising from the scientific advice previously provided by the CVMP under Article 107(6). Implementing condition B (blanket) for this active substance is expected to adequately address the risk to the environment. However, the proposal not to restrict the use to individual animals when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, is not considered to satisfactorily mitigate the risks to animal or public health from AMR associated with the use of difloxacin.

2.3. Danofloxacin and marbofloxacin

The CVMP is asked if other quinolones (difloxacin, enrofloxacin, flumequine, oxolinic acid) were to be included in the list under Article 114(3) without restriction to be used only in individual food-producing aquatic animals, would restricting the use of marbofloxacin and danofloxacin under Article 114(1)(b) and (c) only to individual food-producing aquatic animals no longer have a high impact on animal health, and if not, what would be recommended?

Conclusions arising from the scientific advice under Article 107(6)

The following conclusions were reached within the context of the previous scientific advice under Article 107(6) provided by the CVMP in June 2023 for danofloxacin and marbofloxacin:

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, when using an extemporaneous formulation or when using a human medicinal product, the product should be administered to individual animals, only.

Conclusions arising from the scientific advice under Article 114(3)

The following conclusions were reached within the context of the previous scientific advice under Article 114(3) provided by the CVMP in May 2025 for danofloxacin and marbofloxacin:

- If the substances cannot be used in animals other than individual animals, the impact on animal health is considered high.
- There is only a limited number of antibacterials authorised in food-producing aquatic species. There is a need for several antibacterial substances in case the more commonly used substances are unavailable, and to be able to choose the substance according to situation. The substances are needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species.
- The substances are expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available. If the substances can be used by multiple application methods, the method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect must be selected.
- When possible, any treatment shall take place in a closed system with:

  a) removal or inactivation of the substances in used treatment water or solid waste before discharge into the environment

  b) if (a) is not possible, contaminated water should be released into a recognised wastewater treatment system

  c) if neither (a) nor (b) are possible, dilution of contaminated water so that the substances are present at concentration levels lower than 1µg/L is required before discharge in the environment.

Recommended conditions of use and risk mitigation measure codes: Danofloxacin (B); marbofloxacin (B).

[B: expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available; to be used by the application method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect; when possible, any treatment shall take place in a closed system (see above)].

CVMP view

According to the scientific advice provided by CVMP under Article 114(3), neither danofloxacin nor marbofloxacin were identified by the aquaculture sector as important for the treatment of food-producing aquatic species.

In their request for guidance, the Commission proposes that the implementing act under Article 114(3) includes the condition B (blanket) as reflected by risk mitigation measure code B in the scientific advice under Article 114(3) for danofloxacin and marbofloxacin. That is, use is expected to be harmful to the aquatic environment and therefore such products should only be used if other, less environmentally harmful treatment options are not available. This approach is in line with the previous scientific advice provided by the CVMP and the inclusion of this condition is therefore supported.

The Commission also proposes that the implementing act under Article 114(3) includes the condition S (use restricted to individual animals only) as reflected by risk mitigation measure code S in the scientific advice under Article 114(3) for danofloxacin and marbofloxacin and when expanding the scope of Commission Implementing Regulation (EU) 2024/1973 to food-producing aquatic species:

- to restrict the use of danofloxacin and marbofloxacin under Article 114 of Regulation (EU) 2019/6 to individual animals only in line with the currently included restrictions applicable to

the use of quinolones (including fluoroquinolones) under Articles 112 and 113 of Regulation (EU) 2019/6.

The rationale set out by the Commission for such an approach is based on the fact that currently authorised VMPs containing danofloxacin or marbofloxacin are indicated for individual animal administration only, in cattle and pigs. Consequently, the use of danofloxacin or marbofloxacin in food-producing aquatic species at a group level may represent a significant increase in exposure (and associated risk of AMR).

The previous scientific advice under Article 114(3) states the following in respect of criterion (c) concerning the availability or lack of availability of other medicinal products, treatments or measures for prevention or treatment of diseases or certain indications in food-producing aquatic species: *"There is only limited number of antibacterials authorised in food-producing aquatic species. There is a need for several antibacterial substances in case the more commonly used substances are unavailable, and to be able to choose the substance according to situation. The substance is needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species"*. The advice also states that if the substances cannot be used in animals other than individual animals, the impact on animal health is considered high.

Notwithstanding the above, the CVMP notes that neither danofloxacin nor marbofloxacin were identified by the aquaculture sector as important for the treatment of food-producing aquatic species. Further, danofloxacin and marbofloxacin belong to the same class (fluoroquinolones) as enrofloxacin, flumequine, oxolinic acid and difloxacin and therefore their spectrum of antimicrobial activity (and consequently potential indications for use) in food-producing aquatic species are expected to be similar.

Concerning the Commission's proposal to restrict the use of danofloxacin and marbofloxacin to individual animals only, this is consistent with the previous scientific advice provided by CVMP under Article 107(6) which advised that when the proposed route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product, the product should be administered to individual animals only. That scientific advice stated that there is little or no evidence supporting the efficacy or need for alternative routes of administration in relation to (fluoro)quinolones in farmed animals. Thus, although the impact on farming/aquaculture of restriction to individual animal use cannot be foreseen, it is not expected to be significant. Therefore, the Commission's proposal to restrict the use of danofloxacin and marbofloxacin to individual animals can be supported, does not appear to conflict with the previous scientific advice provided under Article 107(6) and is unlikely to have a high impact on animal health.

The Commission suggests that by implementing condition mitigation measure B (blanket), it is understood that this would not only mitigate against environmental risks but also against AMR risks by minimising exposure.

With reference to the rationales set out in the two previous scientific advices (and noting the different criteria upon which each was based), the CVMP accepts that the implementation of condition B (blanket) mitigates not only environmental risks but is also expected to reduce AMR risks by minimising exposure. Whilst it is agreed that such a risk mitigation measure would be expected to minimise exposure to the aquatic environment, following use of the substance in aquaculture and in particular, assuming that the advice is followed that any treatment shall take place in a closed system when possible, the environment is only one source of exposure to antimicrobial resistance. AMR may also result from exposure to the active substances within treated animals, particularly under group treatment conditions, and it is unknown to what extent this source of risk is mitigated by environmental measures alone. It can be accepted that in the scientific advice provided under Article 107(6), the CVMP also considered (under criteria (a) and (b)) risk to animal or public health if the

antimicrobial is used in accordance with Article 114 and the risk for animal or public health in case of development of AMR.

As indicated above, some risk mitigation measures to limit AMR were included in the previous scientific advice under Article 107(6) for use of (fluoro)quinolones) in food-producing aquaculture animals. These include restricting the administration to individual animals only when the proposed route of administration is outside the terms of the SPC, or when using a human medicinal product or an extemporaneously prepared product. That scientific advice stated that there is little or no evidence supporting the efficacy or need for alternative routes of administration in relation to (fluoro)quinolones in farmed animals. Therefore, although the impact on farming/aquaculture of restriction to individual animal use cannot be foreseen, it is not expected to be significant.

From an environmental perspective, implementing condition B (blanket) for danofloxacin and marbofloxacin is expected to adequately address the risk to the environment and does not appear to conflict with the previous scientific advice provided under Article 107(6).

Given that the risk for the environment identified for danofloxacin and marbofloxacin within the context of the scientific advice under Article 114(3) is likely to be similar and consequently the risk of AMR from the environment may occur as for enrofloxacin, flumequine, oxolinic acid and difloxacin, the CVMP considers that for consistency purposes, when expanding the scope of Regulation (EU) 2024/1973 to Article 114, condition B (blanket) should be imposed for extemporaneously prepared VMPs containing danofloxacin and marbofloxacin as active substance, in line with what is proposed for VMPs containing enrofloxacin, flumequine, oxolinic acid and difloxacin as active substances.

In the scientific advice previously provided under Article 114(3), the CVMP advised that as danofloxacin and marbofloxacin are expected to be harmful to the environment, when possible,

- treatment should take place in a closed system with removal or inactivation of the substance in used treatment water or solid waste before discharge into the environment;

- if this is not possible, contaminated water should be released into a recognised wastewater treatment system;

- if neither of the above are possible, dilution of contaminated water so that the substance is present at a concentration lower than 1 µg/L is required before discharge into the environment.

In conclusion, it can be accepted that in light of the proposal to include enrofloxacin, flumequine, oxolinic acid and difloxacin in the list being prepared under Article 114(3), the inclusion of danofloxacin and marbofloxacin in the list being prepared under Article 114(3), but restricted to use in individual food-producing aquatic animals, is not expected to have a high impact on animal health in terms of availability of alternative substances. Consequently, the set of conditions as proposed by the Commission can be accepted. However, the CVMP considers that for consistency purposes, when expanding the scope of Regulation (EU) 2024/1973 to Article 114, condition B (blanket) should be imposed for extemporaneously prepared VMPs containing danofloxacin or marbofloxacin as active substance, in line with what is proposed for VMPs containing enrofloxacin, flumequine, oxolinic acid or difloxacin as active substance.

2.4. Cefoperazone, cefquinome and ceftiofur

The CVMP is asked whether the proposed set of conditions satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the

use of cefoperazone, cefquinome and ceftiofur under Article 114(1)(b) and (c), and if not, what would be recommended?

Conclusions arising from the scientific advice under Article 107(6)

The following conclusions were reached within the context of the previous scientific advice under Article 107(6) provided by the CVMP in June 2023 for cefoperazone, cefquinome & ceftiofur:

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that 3rd- and 4th-generation cephalosporins are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- Not to be used in food-producing aquaculture.
- To be used in individual animals only. Exemption: Ornamental or conservation aquatic animals kept in closed water tanks.

Conclusions arising from the scientific advice under Article 114(3)

The following conclusions were reached within the context of the previous scientific advice under Article 114(3) provided by the CVMP in May 2025 for cefoperazone, cefquinome & ceftiofur:

- The substances should be used in individual animals only. If the substances cannot be used, the impact on animal health is considered high.
- Combination with beta-lactamase inhibitors is reserved for treatment of certain infections in humans and therefore cefoperazone, cefquinome and ceftiofur should not be used in combination with beta-lactamase inhibitors.
- There is only a limited number of antibacterials authorised in food-producing aquatic species. There is a need for several antibacterial substances in case the more commonly used substances are unavailable, and to be able to choose the substance according to situation. The substances are needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species.
- The substances are not to be used as first choice treatment.
- The substances have some intrinsic properties which indicate a potential risk to the environment, however, there is insufficient information available to conclude that other antimicrobial substances from this group would represent a lower environmental risk.
- The substances are expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available. If the substances can be used by multiple application methods, the method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect must be selected.
- When possible, any treatment shall take place in a closed system with:

  a) removal or inactivation of the substances in used treatment water or solid waste before discharge into the environment

  b) if (a) is not possible, contaminated water should be released into a recognised wastewater treatment system

c) if neither (a) nor (b) are possible, dilution of contaminated water so that the substances are present at concentration levels lower than 1µg/L is required before discharge in the environment.

Recommended conditions of use and risk mitigation measure codes: cefoperazone (B, S, C); cefquinome (B, S, C); ceftiofur (B, S, C).

[B: expected to be harmful to the aquatic environment and must only be used if other, less environmentally harmful treatment options are not available; to be used by the application method that will result in the lowest environmental exposure while achieving a satisfactory therapeutic effect; when possible, any treatment shall take place in a closed system (see above)].

[S: substance shall be used in individual animals only].

[C: substance shall not be used in combination with beta-lactamase inhibitors].

CVMP view

According to the scientific advice provided by CVMP under Article 114(3), cefoperazone, cefquinome and ceftiofur were not identified by the aquaculture sector as important for the treatment of food-producing aquatic species.

In their request for guidance, the Commission proposes that the implementing act under Article 114(3) includes the condition B (blanket) as reflected by risk mitigation measure code B in the scientific advice under Article 114(3) for cefoperazone, cefquinome and ceftiofur. That is, use is expected to be harmful to the aquatic environment and therefore such products should only be used if other, less environmentally harmful treatment options are not available. This approach is in line with the previous scientific advice provided by the CVMP and the inclusion of this condition is therefore supported.

The Commission also proposes that the implementing act under Article 114(3) includes the condition S (use restricted to individual animals only) as reflected by risk mitigation measure code S in the scientific advice under Article 114(3) for cefoperazone, cefquinome and ceftiofur and when expanding the scope of Commission Implementing Regulation (EU) 2024/1973 to food-producing aquatic species:

- to restrict the use of cefoperazone, cefquinome and ceftiofur under Article 114 to individual animals only in line with the currently included restrictions applicable to the use of 3rd and 4th generation cephalosporins under Article and 113 of Regulation (EU) 2019/6. [It is noted that this condition does not apply to use in accordance with Article 112 of Regulation (EU) 2019/6 in aquatic animals kept in closed water tanks i.e. in non-food producing aquatic species].

The rationale set out by the Commission for such an approach is based on the fact that currently authorised VMPs containing cefoperazone, cefquinome and ceftiofur are indicated for individual animal administration only, in cattle, pigs and horses. The CVMP notes that the previous scientific advice provided under Article 107(6) recommended that cefoperazone, cefquinome and ceftiofur should not be used in food-producing aquaculture. The rationale for this was stated as follows: *"Although EFSA does not monitor for antimicrobial resistance in aquaculture food production, ESBLs have been detected in isolates from fish and other species reared in aquaculture systems globally. Considering that aquaculture systems are regarded as potential hotspots for driving emergence, release, transmission and persistence and spread of AMR bacteria and resistance genes, discussed in Section 3.1.2.(iii) of this advice, and the high importance to human and animal health of this antimicrobial class, it is recommended that its use in food-production aquaculture should be restricted."*

Notwithstanding the fact that neither cefoperazone, cefquinome nor ceftiofur were identified by the aquaculture sector as important for the treatment of food-producing aquatic species, the scientific

advice provided under Article 114(3) indicated that there is a need for these substances and states the following in respect of criterion (c) concerning the availability or lack of availability of other medicinal products, treatments or measures for prevention or treatment of diseases or certain indications in food-producing aquatic species: *"There is only limited number of antibacterials authorised in food-producing aquatic species. There is a need for several antibacterial substances in case the more commonly used substances are unavailable, and to be able to choose the substance according to situation. The substance is needed to treat or prevent infectious disease, for which there is lack of availability of other treatments or measures in food-producing aquatic species"*. The advice also states that if the substances cannot be used, the impact on animal health is considered high.

The Commission specifically seeks guidance as to whether the proposed conditions B (blanket) and S (individual animal treatment) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6).

The Commission suggests that by implementing condition mitigation measure B (blanket), it is understood that this would not only mitigate against environmental risks but also against AMR risks by minimising exposure.

With reference to the rationales set out in the two previous scientific advices (and noting the different criteria upon which each was based), the CVMP does not share the view that the proposed condition B (blanket) mitigates not only environmental risks but is also expected to reduce AMR risks by minimising exposure. Whilst it is agreed that such a risk mitigation measure would be expected to minimise exposure to the aquatic environment, following use of the substances in aquaculture and in particular, assuming that the advice is followed that any treatment shall take place in a closed system when possible, the environment is only one source of exposure to antimicrobial resistance. AMR may also result from exposure to the active substances within treated animals, particularly under group treatment conditions, and it is unknown to what extent this source of risk is mitigated by environmental measures alone. It can be accepted that in the scientific advice provided under Article 107(6), the CVMP also considered (under criteria (a) and (b)) risk to animal or public health if the antimicrobial is used in accordance with Article 114 and the risk for animal or public health in case of development of AMR. Based on that assessment, the CVMP recommended that cefoperazone, cefquinome and ceftiofur should not be used in food-producing aquaculture.

The scientific advice provided under Article 114(3) did not specifically consider the development of resistance either as a result of exposure of the environment or the treatment of animals, and the related risks for animal and public health were considered to be outside the scope of that advice. Furthermore, the scientific advice under Article 107(6) stated that no evidence was found for the use of 3rd- and 4th-generation cephalosporins in food-production aquaculture in the EU; therefore, although impacts on aquaculture cannot be fully foreseen, they are not expected to be significant under current circumstances.

In the opinion of the CVMP, the proposed conditions (B and S) do not satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6). Consequently, the CVMP remains of the opinion that cefoperazone, cefquinome and ceftiofur should not be used in food-producing aquaculture and should therefore not be included in the list being prepared under Article 114(3).

Although the scientific advice provided under Article 114(3) recommended that cefoperazone, cefquinome and ceftiofur should not be used in combination with beta-lactamase inhibitors, Commission Implementing Regulation (EU) 2022/1255 already prohibits the use of combinations of cephalosporins with beta-lactamase inhibitors. When expanding the scope of Commission Implementing Regulation (EU) 2024/1973 to include Article 114, the Commission proposes to explain in the recitals that the conditions imposed in Commission Implementing Regulation (EU) 2022/1255

(and other regulations) should be seen as cumulative/complementary. The CVMP can support the Commission's proposal.

It is noted that the Commission also proposes to specify that the conditions in Commission Implementing Regulation (EU) 2024/1973 are without prejudice to the conditions laid down in the implementing act under Article 114(3). It is agreed that the inclusion of such a condition is warranted on the grounds that the scope of that Implementing Regulation is to be expanded to include Article 114 and therefore it is important to ensure coherence with the implementing act under Article 114(3). Consequently, this proposed condition is also supported by CVMP.

In conclusion, the set of conditions as proposed by the Commission are not considered to satisfactorily mitigate the risks to animal or public health from AMR associated with the use of cefoperazone, cefquinome and ceftiofur under Article 114(1)(b) and (c), when taking into consideration the conditions to be included in Commission Implementing Regulation (EU) 2024/1973, arising from the scientific advice previously provided by the CVMP under Article 107(6). Although the Commission asks that if in the negative, what conditions would be recommended, the CVMP considers that in light of the previous scientific advice provided under Art 107(6), there are currently no suitable conditions that would satisfactorily mitigate the identified risks. The proposals to ensure coherence between Commission Implementing Regulation (EU) 2024/1973 and the implementing act under Article 114(3) and to highlight the relevance of other related regulations are considered appropriate and are supported.

3. Conclusion

Following the letter dated 2 December 2025, in which the European Commission requested the EMA's CVMP to provide guidance pursuant to Article 141(1)(f) of Regulation (EU) 2019/6 on scientific issues in relation to Articles 107(6) and 114(3), the CVMP, after a comprehensive review of the related scientific advice and consultation with experts, considers that the following set of conditions and recommendations could satisfactorily mitigate the risk to animal or public health arising from AMR, should the abovementioned substances be used in aquatic food-producing animals.

	Implementing Act under Article 114 (3)	**Amendment of Regulation (EU) 2024/1973**
EC questions	Would the proposed set of conditions (see below) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of **enrofloxacin, flumequine and oxolinic acid** under Article 114(1)(b) and (c)? In the negative, what conditions would be recommended?	
EC proposal	1. Enrofloxacin, flumequine, oxolinic acid to be included in the list with the proposed condition B (blanket).	2. Not to restrict the use of enrofloxacin, flumequine, oxolinic acid to individual animals only. 3. To impose condition B (blanket) to the use of extemporaneous VMPs containing the three substances.
CVMP feedback	1. Supported, noting that condition B primarily addresses environmental exposure and it is unknown to what extent it mitigates all sources of AMR risk.	2. CVMP does not support not restricting the use of enrofloxacin, flumequine and oxolinic acid to individual food-producing aquatic animals only, when the route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product.

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
		The CVMP considers that in light of the previous scientific advice provided under Art 107(6), the conditions to adequately mitigate the risk of AMR arising from the use of this antimicrobial class in aquaculture, have already been identified in the scientific advice under Article 107(6). 3. CVMP supports to impose the blanket condition for the use of extemporaneously prepared VMPs containing enrofloxacin, flumequine or oxolinic acid.

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
EC questions	Would the proposed set of conditions (see below) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of **difloxacin** under Article 114(1)(b) and (c)? In the negative, what conditions would be recommended?	
EC proposal	1. Difloxacin to be included in the list with the proposed condition B (blanket).	2. Not to restrict the use of difloxacin to individual animals only 3. To impose condition B (blanket) to the use of extemporaneous VMPs containing difloxacin.
CVMP feedback	1. Supported, noting that condition B primarily addresses environmental exposure and it is unknown to what extent it mitigates all sources of AMR risk.	2. CVMP does not support not restricting the use of difloxacin to individual food-producing aquatic animals only, when using an extemporaneously prepared formulation or when using a human medicinal product. The CVMP considers that in light of the previous scientific advice provided under Art 107(6), the conditions to adequately mitigate the risk of AMR arising from the use of this antimicrobial class in aquaculture, have already been identified in the scientific advice under Article 107(6). 3. CVMP supports to impose the blanket condition to the use of extemporaneously prepared VMPs containing difloxacin.

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
EC questions	If other quinolones (difloxacin, enrofloxacin, flumequine, oxolinic acid) were to be included in the list under Article 114(3) without restriction to be used only in individual food-producing aquatic animals, would you consider that restricting the use of **marbofloxacin and danofloxacin** under Article 114(1)(b) and (c) only to individual food-producing aquatic animals no longer has a high impact on animal health? In the negative, what would be recommended?	

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
EC proposal	1. danofloxacin and marbofloxacin to be included in the list with: - condition B (blanket) and - condition S (use restricted to individual animals only).	2. The restrictions to use in individual animals only, which, by virtue of Commission Implementing Regulation (EU) 2024/1973, are currently applicable to the use of *Quinolones (including Fluoroquinolones*) under Articles 112 and 113 of Regulation (EU) 2019/6, to apply also to the uses of danofloxacin and marbofloxacin under Article 114.
CVMP feedback	1. Supported, noting that condition B primarily addresses environmental exposure and it is unknown to what extent it mitigates all sources of AMR risk.	2. CVMP supports to restrict the use of danofloxacin and marbofloxacin to individual food-producing aquatic animals only, when the route of administration is outside the terms of the SPC, when using an extemporaneously prepared formulation or when using a human medicinal product. CVMP considers that for consistency purposes, when expanding the scope of Regulation (EU) 2024/1973 to Article 114, condition B (blanket) should also be imposed for extemporaneously prepared VMPs containing danofloxacin or marbofloxacin as active substance.

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
EC questions	Would the proposed set of conditions (see below) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of **cefoperazone, cefquinome and ceftiofur** under Article 114(1)(b) and (c)? In the negative, what conditions would be recommended?	
EC proposal	1. Cefoperazone, cefquinome, ceftiofur to be included in the list with: - condition B (blanket) and - condition S (use restricted to individual animals only). Note: Commission Implementing Regulation (EU) 2022/1255 already prohibits the use in all animals of cefoperazone, cefquinome, ceftiofur in combination with beta-lactamase inhibitors.	2. 3rd- and 4th-generation cephalosporins to be allowed for use only in individual food-producing aquatic animals. 3. To specify that the conditions in Commission Implementing Regulation (EU) 2024/1973 are without prejudice to the conditions laid down in the implementing act under Article 114(3). 4. To explain in the recitals that the conditions imposed by the various regulations, such as Commission Implementing Regulation (EU) 2022/1255, should be seen as cumulative/complementary.
CVMP feedback	1. In the opinion of the CVMP, the proposed conditions (B and S) do not satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6). Consequently, the CVMP remains of the opinion that cefoperazone, cefquinome and ceftiofur should not	2. In the opinion of the CVMP, restricting the use of cefoperazone, cefquinome and ceftiofur to individual food-producing aquatic animals only, is not considered to satisfactorily mitigate the risks to animal or public health from AMR associated with their use under the cascade.

	Implementing Act under Article 114 (3)	Amendment of Regulation (EU) 2024/1973
	be used in food-producing aquaculture and should therefore not be included in the list being prepared under Article 114(3). The CVMP considers that in light of the previous scientific advice provided under Art 107(6), there are currently no suitable conditions that would satisfactorily mitigate the identified risks.	3. and 4. The proposals to ensure coherence between Commission Implementing Regulation (EU) 2024/1973 and the implementing act under Article 114(3) and to highlight the relevance of other related regulations are considered appropriate and are supported.

References

Commission Implementing Regulation (EU) 2022/1255 of 19 July 2022 designating antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council, available from: https://eur-lex.europa.eu/eli/reg_impl/2022/1255/oj/eng

Commission Implementing Regulation (EU) 2024/1973 of 18 July 2024 establishing a list of antimicrobials which shall not be used in accordance with Articles 112 and 113 of Regulation (EU) 2019/6 of the European Parliament and of the Council or which shall only be used in accordance with those Articles subject to certain conditions, available from: https://eur-lex.europa.eu/eli/reg_impl/2024/1973/oj

EMA/CVMP/151584/2021, Scientific advice under Article 107(6) of Regulation (EU) 2019/6 for the establishment of a list of antimicrobials which shall not be used in accordance with Articles 112, 113 and 114 of the same Regulation or which shall only be used in accordance with these articles subject to certain conditions, available from: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/vet_reg_cascade_list_report_en.pdf

EMA/CVMP/29892/2024, Scientific advice under Article 114(3) of Regulation (EU) 2019/6 on veterinary medicinal products - List of substances used in veterinary medicinal products authorised in the Union for use in food-producing terrestrial animal species or substances contained in medicinal products for human use authorised in the Union, which may be used in food-producing aquatic species in accordance with Article 114(1) (), available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/scientific-advice-under-article-1143-regulation-eu-2019-6-veterinary-medicinal-products-list-substances-used-veterinary-medicinal-products-authorised-union-use-food-producing-terrestrial-animal_en.pdf

European Parliament and Council of the European Union, 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, available from: https://eur-lex.europa.eu/eli/reg/2019/6/oj