Use of VMPs outside terms of MA

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1. Regulation (EU) 2019/6

- MA required for the placing on the market of VMPs in the Union.
- The terms of the MA reflect **what has been scientifically demonstrated in terms of quality, safety and efficacy**.
- Post-marketing setting: MAHs and CAs to amend/suspend/withdraw MA if terms thereof are not conductive to a safe or efficacious use.

1. Regulation (EU) 2019/6 (cont)

- Art. 106(1): VMPs are to be used in accordance with the terms of the MA.
- However, this is not an absolute principle: veterinarians can depart from terms of MA under conditions established in Articles 112-114 (“cascade use”).

Other considerations

- Warnings are not contraindications. They are intended to provide information to the veterinarians.
- Where SPC allows for flexibility as regards dosage regime, such adaptation is according to the MA.

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2. “Cascade use”

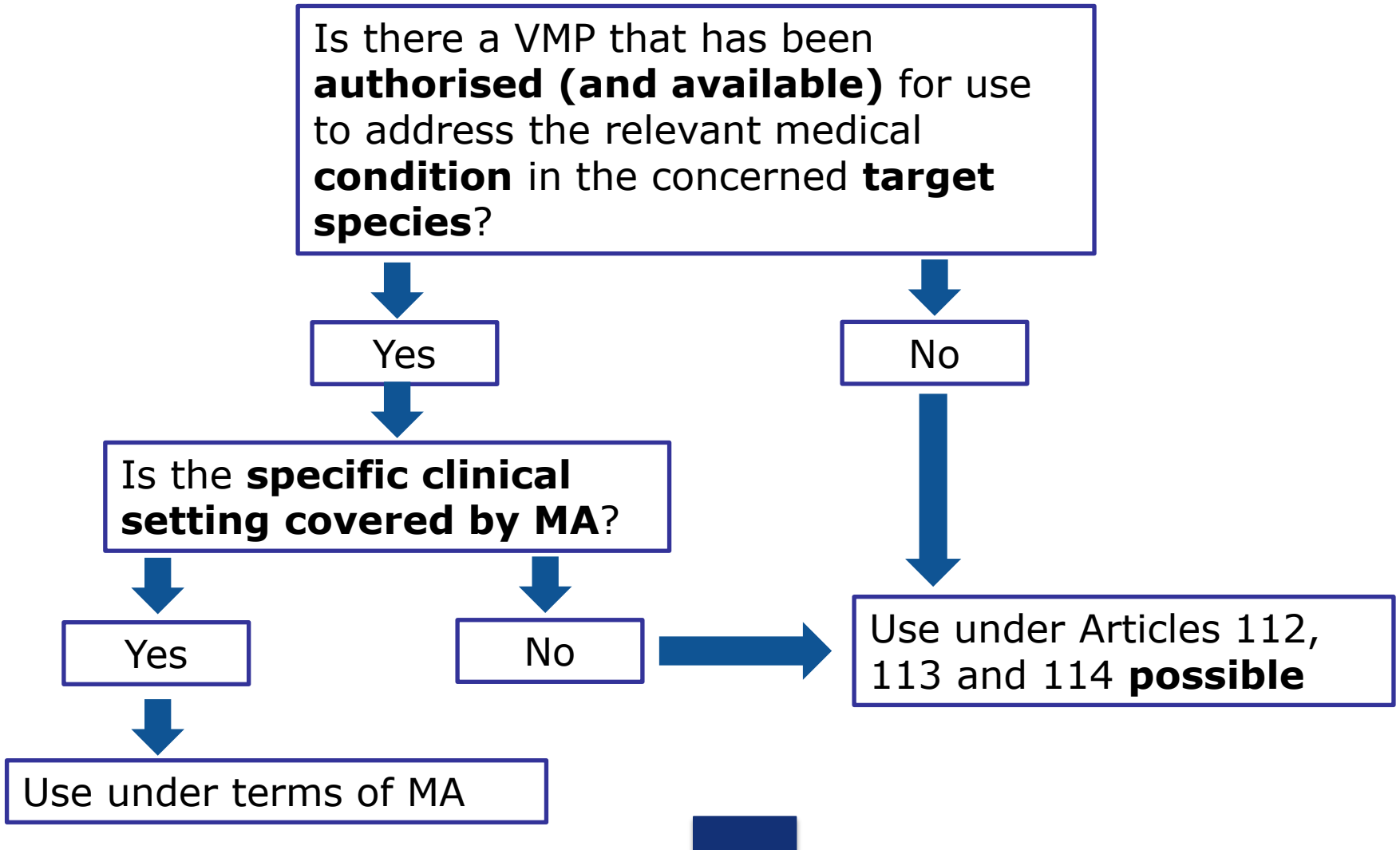
- The cascade use addresses **animal health/welfare needs** that are **not specifically covered by an authorised VMP** or when the relevant authorised VMP is **not available**.
- Key elements in the cascade use:
  - Not a general route (“exceptionally”).
  - Specific unmet needs (“in particular to avoid causing unacceptable suffering”).
  - Under the veterinarian’s personal responsibility.

2. “Cascade use” (cont)

- The cascade use enables veterinarians to depart from the terms of an existing MA (“by way of derogation from Article 106(1)”).
- Articles 112-114 provide for the use of a VMP that has been authorised in accordance with the Regulation for use **in the same animal species** or in another species* **for the same indication** or another indication.

*In case of food-producing animals, the VMP should have been authorised for the treatment of a food producing species.

2. Cascade use (cont)



A. Uses allowed under cascade*

*Based on examples examined.

Adjustments of dosage regime

- Adjustment to specific populations where the MA does not specifically reflect the **specific subset** (*e.g.* new born, pregnant, very old animals).
- Adjustment in case of **underlying health condition/circumstances** of treated animal not specifically reflected in the MA (*e.g.* renal or liver impairment, gastrointestinal ulcer, hypersensitivity).

Adjustments of dosage regime (cont)

- Adjustment in case of **concomitant use** with other VMPs (*e.g.* use of several VMPs for pain relief or for sedation).
- Adjustment following signals that treated animal does **not** adequately **respond** (*e.g.* pain relief, dermatitis, ulcer)
- Adjustment to **address side effects**.

B. Uses that may be allowed under the cascade (depending on availability of alternatives)*

*Based on examples examined.

Adjustments of dosage regime

- Adjustment to treat a **more severe condition** than the one specifically provided for in the MA (*e.g.* pain relief setting, sedation for long procedures).
- *Are there VMPs authorised and available for the more severe condition?*
  - Yes: VMP specifically authorised should be used.
  - No: adjustment of dose under cascade is possible

Different route of administration

- The authorised **route of administration is not compatible with the specific needs/circumstances of the treated animal** (*e.g.* IV in non-cooperative animals).
- *Are there VMPs authorised and available with the route of administration needed?*
  - Yes: VMP specifically authorised should be used.
  - No: use under cascade is possible.

Use that is contraindicated

- Use in a subset of the population that is specifically **contraindicated** in MA.
  - Contraindications reflect scientific evidence.

- Are there VMPs authorised and available for the relevant condition and subset?
  - Yes: VMP specifically authorised should be used.
  - No: use under cascade is possible (professional judgement and responsibility of veterinarian).

Modified vaccination schedule

- Compliance with **regulatory requirements** (*e.g.* governing movement of horses).
- *Are there VMPs authorised and available with the required vaccination schedule?*
  - Yes: VMP specifically authorised should be used.
  - No: use under cascade is possible.

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3. Reported concerns as regards the use of VMPs under terms of MA

- The vast majority of concerns/examples raised were assessed.
- All of them were found to fit under current legal framework, which includes the cascade use.
- The issues presented below correspond to examples provided where additional information was requested.

3. Reported concerns as regards the use of VMPs under terms of MA (cont)

Three type of issues raised

- Discrepancy with international recommendations.
- Therapeutic goal is achieved with lower doses.
- Higher dosages recommended in literature.

A. Discrepancy with international recommendations.

Issue: Authorised vaccines for dogs and cats do not comply with international vaccination recommendations

General remarks

- SPCs based on quality, safety and efficacy demonstrated for the specific vaccine.
- Use of serological testing and adaptation according to the outcome is possible under the cascade (adaption to the underlying health condition/circumstances of the animal).
- WSAVA recommendations are not binding: the need to adapt the recommendations to the specific situation of different regions specifically acknowledged.

Issue: Authorised vaccines for dogs and cats do not comply with international vaccination recommendations

- **Interference of maternal antibodies**
  - Where not addressed in SPC, adaptation of dosage regime in accordance with cascade is possible (adaptations necessary to address specific clinical needs of animal subset).
- **Duration of immunity of vaccines can be longer than provided in SPCs**
  - Duration of immunity in SPC is minimum duration demonstrated.
- **Mandatory vaccination requirements (legal)**
  - Cascade use is possible.

Issue: Authorised vaccines for dogs and cats do not comply with international vaccination recommendations

Example 1:

For the active immunisation of puppies from 4 weeks of age onwards to prevent clinical signs and mortality of canine distemper virus infection and canine parvovirus infection and to prevent viral excretion following canine distemper virus infection and following canine parvovirus infection.

Onset of immunity: for canine distemper virus: 7 days;
for canine parvovirus: 3 days.

Duration of immunity: 8 weeks.

Special precautions for safe use in the target species:
Moderate to high levels of maternally derived antibodies against canine distemper virus can reduce the efficacy of the product against canine distemper.

It is typically advised that each pup is vaccinated with this product at 6 weeks of age. In cases where there is a high risk of canine parvovirus infection and/or canine distemper virus infection, it is advised that pups are vaccinated earlier, but not before 4 weeks of age. The routine vaccinations with core vaccines against canine distemper, canine parvovirosis, canine contagious hepatitis and respiratory disease caused by adenovirus type 2 infection should be given as indicated in the package leaflets of these products.

Issue: Authorised vaccines for dogs and cats do not comply with international vaccination recommendations

Example 2:

Active immunisation of cats from eight weeks of age against feline leukaemia for the prevention of persistent viraemia and clinical signs of the related disease.

Onset of immunity:
3 weeks after the primary vaccination.

Duration of immunity:
After the primary vaccination course, the duration of immunity lasts for one year.

Following a first booster vaccination one year after the primary vaccination course, a duration of immunity of 3 years has been demonstrated.

- first injection in kittens from eight weeks of age
- second injection 3 or 4 weeks later.

Maternally derived antibodies can negatively influence the immune response to vaccination. In such cases where maternally derived antibodies are expected, a third injection may be appropriate from 15 weeks of age.

Re-vaccinations:
Following a first booster vaccination one year after the primary vaccination course, subsequent vaccinations can be performed at intervals of three years.

Issue: short-term protocols for hormonal medicinal products for reproductive management in small ruminants not possible

General remarks

- SPCs based on quality, safety and efficacy demonstrated for the specific VMP.
- International guidelines not provided but studies on validity of short-term protocols published in literature.

Issue: short-term protocols for hormonal medicinal products for reproductive management in small ruminants not possible

- Only two examples of SPCs provided: one of them allows for short-term protocol.
- Few products authorised for reproductive management in small ruminants; in case of not available VMPs, cascade use applies.

B. Therapeutic goal is achieved with lower doses

Issue: Medetomidine (sedation or pre-medication prior to anaesthesia in dogs and cats): therapeutic goal achieved at lower dosages

General remark

- A problem with authorised dosages cannot be identified on the basis of pharmacovigilance data.
  - LEE reports expected to increase if dosage is lowered.

- SPC addresses the need for adjustment when used with other antidepressants.

Issue: Medetomidine (sedation or pre-medication prior to anesthesia in dogs and cats): therapeutic goal achieved at lower dosages

- **Adverse conditions linked to underlying conditions/circumstances of treated animal (e.g. cardiac, renal impairment):** can be addressed under the cascade.

- **Concomitant use with other VMPs:** can be addressed under the cascade.

Issue: Trilostane (pituitary and adrenaline-dependent hyperadrenocorticism in dogs): therapeutic goal achieved at lower dosages

General remarks

- A problem with authorised dosage regime cannot be identified on the basis of pharmacovigilance data.
  - However, there are some signals under close monitoring.

- SPCs contain provisions allowing for flexible use:
  - *The lowest possible dose to control the clinical symptoms should be used.*
  - *Titrate the dose according to individual response.*

Issue: Trilostane (pituitary and adrenaline-dependent hyperadrenocorticism in dogs): therapeutic goal achieved at lower dosages

- Adaptations of dosage regime for **animals not responding to treatment** are possible under cascade.
- Adaptations of dosage regime to **specific health conditions of the treated animal** are possible under the cascade.

C. Higher dosages recommended in literature

Issue: Phenylpropanolamine (treatment of urinary incontinence in dogs) higher doses recommended in literature.

- LEE signal (submitted by MAH) currently under assessment.
- Dose regime adjustment following **signals that treated animal does not adequately respond** are possible under the cascade.

Issue: Prednisolone (inflammatory and immune conditions in dogs and cats): higher doses recommended in literature.

General remarks

- A problem with authorised dosages cannot be identified on the basis of pharmacovigilance data.
- Publication reported addresses immune thrombocytopenia:
  - not appropriate to extrapolate dosages to all inflammatory or immune-mediated diseases;
  - recommended starting dose (in the publication) is consistent with the SPC for this specific indication.
- Some SPCs provide for higher dosages or flexible dosing.

Issue: Prednisolone (inflammatory and immune conditions in dogs and cats): higher doses recommended in literature.

- Adjustments of dosage regime are possible under the case if:
  - **VMPs not available for the specific clinical need** (*e.g.* severe immune-mediated diseases).
  - Adaptation is required to address specific **health conditions/circumstances of treated animal health**.
  - Adjustment following **signals that treated animal does not adequately respond**.

Issue: Telmisartan (chronic kidney disease in cats): higher dosages recommended in IRIS guidelines

General remark

- A problem with authorised dosage cannot be established on the basis of pharmacovigilance data.

Issue: Telmisartan (chronic kidney disease in cats): higher dosages recommended in IRIS guidelines

- Adjustment of dosage regime following **signals that treated animal does not adequately respond** is possible under the cascade.
- Adjustment of dosage regime to address **specific clinical needs of a subset of the targeted population** is possible under the cascade.

4. Antiparasitics:

- Different views expressed:
  - Experience showing better efficacy profile with lower dose and extended period of time.
  - Shorter treatment periods preferable.
  - Indications that current dosages are too low and pose a risk of resistance.

Antiparasitics (cont)

The floor is yours…

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Guiding principles

- **Specific clinical needs** of animals not addressed under an existing MA can be handled under the cascade.

Guiding principles (cont)

- Safety or efficacy concerns as regards the **general application** of the terms of a MA cannot be addressed under the cascade:
  - Responsibility of MAH and CAs to ensure the positive benefit/risk of VMPs under the conditions of use specified in the terms of the MA.
  - Efficacy or safety concerns when using VPMs in accordance with terms of the MA should be reported by veterinarians.

Thank you!