Guidance to Applicants

SANTE VETERINARY MEDICINES
DG Health and Food Safety

Disclaimer:

The Commission's interpretation on certain provisions of Regulation (EU) 2019/6 has been provided in the Guidance to Applicants. Any views expressed today cannot be attributed to the Commission but are only the personal views of the presenter.

Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Overview

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I. General issues

1. "Veterinary medicinal product"

(1) 'veterinary medicinal product' means any substance or combination of substances which fulfils at least one of the following conditions:

(a) it is presented as having properties for treating or preventing disease in animals;

(b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

(c) its purpose is to be used in animals with a view to making a medical diagnosis;

(d) its purpose is to be used for euthanasia of animals;

(19) 'benefit-risk balance' means an evaluation of the positive effects of the veterinary medicinal product in relation to the following risks relating to the use of that product:

(a) any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;

(b) any risk of undesirable effects on the environment;

(c) any risk relating to the development of resistance;

1. “Veterinary medicinal product” (cont.)

- The **definition** of “**veterinary medicinal product”** in the Regulation **corresponds to the definition in Directive 2001/82/EC**, **with the exception of substances or combination of substances intended to be used for euthanasia**.
- The inclusion of substances -or combinations of substances- intended for euthanasia within the definition of “veterinary medicinal product” is the reason for which, in the context of the definition of “benefit-risk balance”, the Regulation refers to “positive effects” instead of “positive therapeutic effects”, which was the term used in Directive 2001/82/EC.
- **The concept of “benefit” under the Regulation should continue to be interpreted in the light of the definition of “veterinary medicinal product**”.

1. "Veterinary medicinal product" (cont.)

- **Presentational criteria**: the product is indicated or recommended for treating or preventing a disease, *e.g.* by means of labels, leaflets or other representations.
- **Functional criteria**: Products designed to restore, correct or modify physiological functions by means of a pharmacological, immunological or metabolic mode of action:
  - Potential use for treatment of a **recognised pathological condition**; and
  - The product is potentially capable of inducing a **significant effect** on physiological functions.

1. “Veterinary medicinal product” (cont.)

Veterinary medicinal products for zootechnical purposes:

A veterinary medicinal product for zootechnical purposes is a product that is administered to a **healthy animal for an indication related to the reproductive system**, including oestrus synchronisation, termination of unwanted gestation or the preparation of donors and recipients for the implantation of embryos. Products qualifying as such were covered by the Directive 2001/82/EC and continue to be covered by the Regulation as the definition of “veterinary medicinal product” is unchanged in this regard.

2. Centralised procedure

- **<u>Mandatory scope of centralised procedure:</u>** For veterinary medicinal products listed in art. 42(2)*, use of the centralised procedure is compulsory.
- The mandatory scope of the centralised procedure also applies to generic applications.
  - If the reference product was centralised authorised because it contained a NAS; a generic application under national route is however possible (no longer NAS).

* With the exception of veterinary medicinal products covered under para(3).

2. Centralised procedure (cont.)

- If during the assessment procedure of an application submitted to the national competent authorities, it becomes apparent that the veterinary medicinal product falls under the scope of the centralised procedure, **the national procedure cannot continue**.
- Prospective applicants having doubts as to whether a veterinary medicinal product may fall under the scope of the centralised procedure are **advised to consult** the relevant competent authorities prior to submitting an application under the national procedure.

3. Centralised v. national procedures

- **No coexistence of national and centralised routes:** The use of the national and the centralised procedure for the **same veterinary medicinal product** by the **same marketing authorisation holder/applicant** is not possible.

- What remains possible:
  - Centralised MAA for a generic of a nationally authorised product, provided that applicant does not hold a national MA for the same product.
  - National MAA for a generic of a centrally authorised product (except mandatory scope), provided that applicant does not hold a centralised MA for the same product.

4. Same VMP

- Any medicinal product with the **same qualitative and quantitative composition in active substances** (i.e. the same strength) and the **same pharmaceutical form** is to be considered as the same medicinal product.
- This definition is relevant to the interplay between the centralised and the national procedures as well as in connection with the operation of the decentralised, mutual recognition or subsequent recognition procedures.

5. Same applicant/MAH

- Applicants and marketing authorisation holders **belonging to the same company group or that are controlled by the same physical or legal entity** are to be considered as one entity; and
- Applicants and marketing authorisation holders that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/marketing authorisation holder if they have concluded tacit or explicit **agreements concerning the marketing of the same veterinary medicinal product**. This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same veterinary medicinal product in exchange for fees or other considerations.

II. MAAs

1. The concept of LM

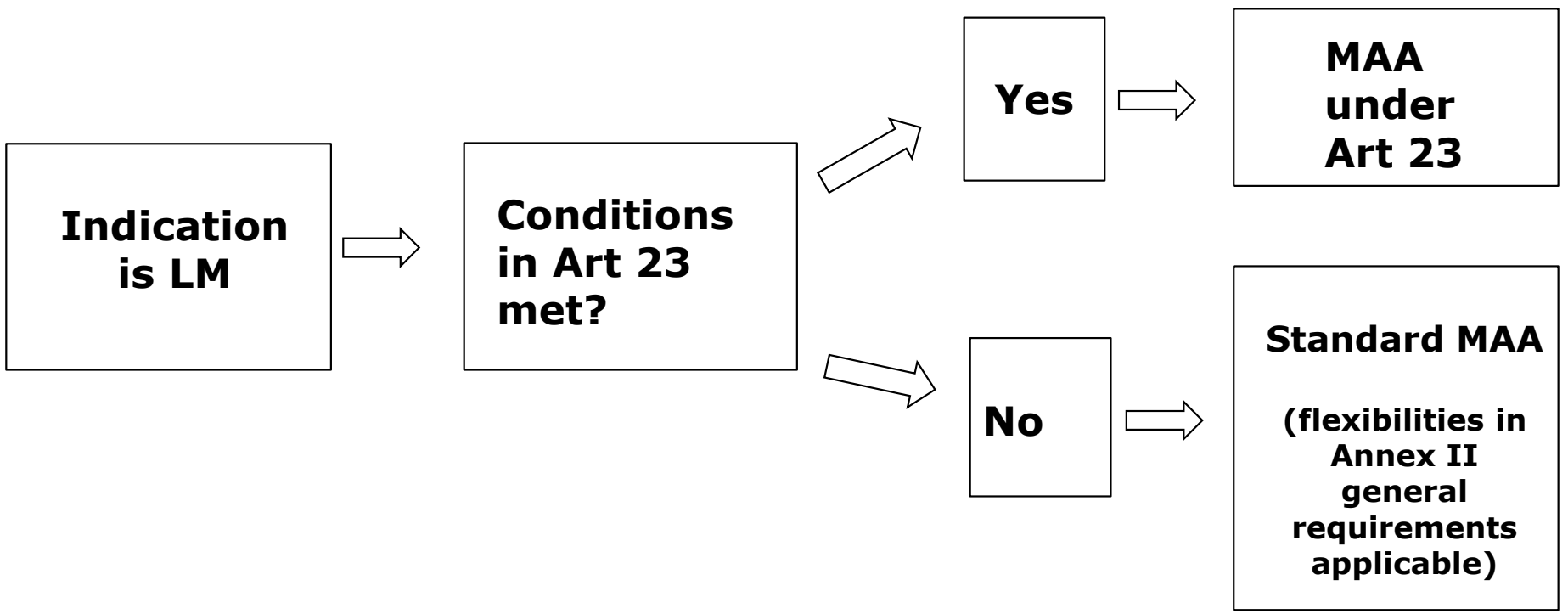
(29) 'limited market' means a market for one of the following medicinal product types:

(a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas;

(b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats;

1. The concept of LM (cont.)

- The determination whether a veterinary medicinal product is intended for the treatment or prevention of disease that occurs infrequently or in limited geographical areas should be done on the basis of **epidemiological** criteria, **scientific** criteria and **current veterinary practice**.
- Applications for artificially **restrictive indications cannot be accepted** by the competent authorities in the context of applications under art. 23.


Indication is LM
Conditions in Art 23 met?
Yes
MAA under Art 23
No
Standard MAA
(flexibilities in Annex II general requirements applicable)

1. Art. 23: conditions for MAA

1. By way of derogation from point (b) of Article 8(1), the applicant shall not be required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the following conditions are met:

(a) the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided;

(b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.

- The **benefit to animal or public health** of the availability on the market of the veterinary medicinal product **outweighs the risks inherent in the lack of comprehensive data:**
  - **Serious debilitating** or **life-threatening** disease **and unmet medical need**.

1. Art 23: conditions for MAA (cont.)

➢ Unmet medical need:

- A disease for which there exists no satisfactory method of diagnosis, prevention or treatment **authorised** (in the Union) or, even if such a method exists, in relation to which the veterinary medicinal product concerned brings a **meaningful advantage.**

➢ Meaningful advantage:

- It should relate to the **intrinsic properties of the veterinary medicinal product**; and
- **meaningful improvement of efficacy or clinical safety**; exceptionally: major improvement to the care of the treated animals.

➢ VMPs already authorised:

- If VMP(s) authorised centrally, art 23 MAA only possible if there is a meaningful advantage.
- If VMP(s) authorised in one or more MS, art 23 applications may be possible in other MS, provided that no circumvention of MRP/SRP.
- If existing VMP(s) authorised under art 23 or 25, other art 23 MAAs remain possible.

1. Art 23 MAA: miscellanea

- Data requirements that can't be waived:
  - Quality;
  - MRLs;
  - GMO-related data;
  - Antimicrobial resistance data.
- To obtain a MA, a **positive benefit-risk balance should be demonstrated**.
  - The definition of benefit-risk balance set out in point (19) of art. 4(1) of the Regulation is applicable to all marketing authorisations, including those granted under art. 23.
- No coexistence of indications granted under art. 23 with indications granted on the basis of a comprehensive dossier.

2. Generic applications

(9) 'generic veterinary medicinal product' means a veterinary medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference veterinary medicinal product, and with regard to which bioequivalence with the reference veterinary medicinal product has been demonstrated;

(8) 'reference veterinary medicinal product' means a veterinary medicinal product authorised in accordance with Article 44, 47, 49, 52, 53 or 54 as referred to in Article 5(1) on the basis of an application submitted in accordance with Article 8;

2. Generics: the Reference VMP

- MA granted on the basis of **comprehensive technical documentation.**
- **Informed consent MA**.
- **Bibliographic MAs**, provided period of protection of the dossier has expired:
  - Data in public domain can be used by any applicant anytime to compile a distinct dossier; however, the specific dossier submitted under art. 22 is protected.
- **MA granted under art. 23 or art. 25**:
  - Conditions laid down in the respective articles are met (*e.g.* prevalence criteria & unmet medical need in case of LM).
  - Possibility to impose obligations (mirroring obligations in MA of the reference VMP).
  - In case of non-renewal, appropriate action can follow re: generics.

2. Generics: the Reference VMP (cont.)

- **Generic** and **hybrid MAs:**
  - **In principle**, the safety and efficacy of a veterinary medicinal product cannot be established by reference to a veterinary medicinal product that, in turn, roots its safety and efficacy in the demonstration of bioequivalence to a third product. This is because, **in a "generic to a generic" construction, it cannot be inferred that there is a sufficient degree of bioequivalence** between the "generic to the generic" and the original reference veterinary medicinal product.

A veterinary medicinal product that is authorised on the basis of its bioequivalence to another product can only be accepted as reference veterinary medicinal product in the **exceptional cases where the risk of generic drift can be discarded**. In particular, this approach can be accepted in respect of products that have the **same qualitative composition in active substances, are part of the same development and are held by the same marketing authorisation holder.**

2. Generics: the Reference VMP (cont.)

- Reference VMP **is or has been authorised** in the Union, in accordance with Union law.
  - Bioequivalence to be conducted with batches authorised in the Union. If no longer available: hybrid or bibliographic applications remain possible.
- No generic application possible if the reference product has been withdrawn on grounds related to public/animal health or the environment.
- Withdrawal of MA with a view to hinder access of generics may constitute a breach of competition rules.
  - The "autogeneric" can be used as reference VMP unless risk of generic drift.

2. Generic applications: other considerations

- **Bioequivalence:** Where bioequivalence cannot be demonstrated through bioavailability studies and a waiver is not applicable, a MA under Art 19 can only be granted if sufficient data to demonstrate efficacy/safety is provided.
  - Significant technical documentation may be required.

- **Biologicals**: Where the reference product is a biological, a hybrid application should be submitted, unless starting and raw materials and production and controls are the same.

- **Autogenerics**: Requirements in Article 18 should be met (*i.e.* the period of protection of technical documentation has expired or is due to elapse in <2 years).

2. Generics: product information

➢ **Product information**:

The product information of the generic VMP should be **essentially similar** to that of the reference VMP. Differences possible in the following cases:

- Reference VMP is not harmonised.
- Information linked to quality differences (e.g. excipients).
- Aspects in MA of reference VMP covered by patent law or data protection.
- Information about environmental risks and RMMs (when reference product authorised before 1 Oct 2005).*
- Information about the risk of developing AMRs/antiparasitic resistance and RMMs (when reference product authorised before 28 January 2022).*

*Expected to be temporary: duty to update product information under Article 58.

3. Informed consent applications

- An art. 21 MAA cannot be submitted in parallel with the MAA of the cross-referred product.
- Where the cross-referred product has been authorised under art. 23 or art. 25:
  - Obligations may be imposed (mirroring obligations in MA of the reference VMP).
  - In case of non-renewal, appropriate action can follow re: MA granted under art. 21.
- Where the cross-referred product has been authorised before 1 October 2005, **ERA may be required**.

4. Bibliographic applications

- Bibliographic data must be relevant and sufficient:
  - when the safety and efficacy profile of the relevant veterinary medicinal product is determined by the manufacturing process and the starting materials (notably, for **biologicals**), **only literature data that refers to veterinary medicinal products manufactured according to the same procedure** can be considered, **provided that differences in the starting materials do not have an impact on the safety and/or efficacy**. For example, for veterinary medicinal products containing cells subject to substantial manipulation, an application under art. 22 is not acceptable unless the manufacturing process of the product reported in the literature and the manufacturing process of the product covered by the application is the same.

III. Protection of technical documentation

1. General principles

In applying the provisions on the protection of technical documentation of the Regulation account must be taken of the **need to reward major investments** by developers of veterinary medicinal products, the need to ensure **fair access of generics** to the market to increase availability of veterinary medicinal products, and the need to **avoid -as much as possible- disharmonisation in the product information between reference veterinary medicinal products and generics, in particular on aspects of product information that are relevant to public or animal health or the environment.**

1. General principles (cont.)

- **Responsibility of applicant**: it is the responsibility of applicants to ensure that the period of protection of technical documentation relied upon in their applications has elapsed or is due to elapse in less than two years (unless a letter of access is provided).
- **Role of competent authorities**:
  - CAs should reject applications in breach of data protection rules but primary focus on the assessment is Q/S/E.
  - Owners of technical documentation can seek remedies before national courts.

2. "Same marketing authorisation"

- Article 38(3) of Regulation 2019/6:

  "A marketing authorisation or a variation to the terms of a marketing authorisation differing from the marketing authorisation previously granted to the same marketing authorisation holder ***only with regard to target species, strengths, pharmaceutical forms, administration routes or presentations*** *shall be regarded as the same marketing authorisation as the one previously granted to the same marketing authorisation holder for the purpose of applying the rules of the protection of technical documentation."*

2. "Same marketing authorisation" (cont.)

- The concept of SMA concerns variations and marketing authorisations granted to the same holder and is **not applicable across different marketing authorisation holders**.
- The SMA contains the **initial authorisation as well as subsequent changes** thereto regarding target species, strengths, pharmaceutical forms, administration routes or presentations, **also when the subsequent modifications are authorised under a separate marketing authorisation procedure and regardless of the legal basis of the respective applications**.

2. "Same marketing authorisation" (cont.)

- The following is not covered under the SMA:
  - **New indications**.
  - **Combinations of active substances**.
  - **Single active substance** (vis-à-vis a previous combination of active substances).
  - Modifications of active substance amounting to **NAS**.
    - Requests for NAS status to be submitted with the application containing the modified substance.

3. New active substance

A new chemical, biological or radiopharmaceutical veterinary active substance includes:

(i) a chemical, biological or radiopharmaceutical substance not previously authorised as active substance in a veterinary medicinal product in the European Union, and

(ii) a chemical, biological or radiopharmaceutical substance previously authorised as active substance in a veterinary medicinal product in the European Union provided that the following conditions are met:

— For chemical substances: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as active substance in a veterinary medicinal product in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised.

— For biological substances: a biological substance previously authorised as active substance in a veterinary medicinal product in the European Union but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process.

For immunological veterinary medicinal products: The replacement or addition of a new antigen or a new strain in the case of already authorised immunological veterinary medicinal products should not be considered as replacing/adding a new active substance. New isolates or variants of microorganisms that have been authorised in an immunological veterinary medicinal product are likewise not to be considered as new active substances.'

4. Counting the period of protection

Period of protection depends on target species within SMA

Max: 18 years

Date when first MA is granted

New strength/pharma form/route of administration= no extension of protection*

New target species (three years prior to expiry date)= extension of protection

***Unless Article 40(5) applies.**

4. Counting the period of protection (cont.)

- If the initial marketing authorisation concerns a **mix of major and minor target species**, the period of protection that should be applied first is the one set out in Article 39(1)(a).
- The extension of protection set out in Article 40(1) and (2) should be added subsequently.
- The maximum period of protection of 18 years set out in Article 40(3) applies.

5. Target species

- For the purposes of applying the rules on the protection of technical documentation, the concept of target species is to be interpreted on the basis that **sub-types (breeds) or subcategories within a given target species** are **not considered different target species**.

6. Indications

- Technical documentation underpinning the addition of a **new indication** is entitled to a new, stand-alone period of protection.
- However, technical documentation to **confirm, update or modify the product information concerning an existing indication** is not entitled to protection, *e.g.*:

- Technical documentation submitted to support changes to the product information that are intrinsically linked to a given indication, such as **new dosage***, **duration of treatment**, **place in therapy** (e.g. first line, second line), as well as other aspects of the product information relevant to the safe and efficacious use of the product within the relevant indication (*e.g.* information on **concomitant treatments** or onset or duration of effect) are captured by the period of protection of the relevant indication.

*unless art. 40(5) applies.

6. Indications (cont.)

- The addition of a new indication **does not prolong or restart the duration of the protection of the SMA**.
  - The period of protection concerns exclusively the documentation supporting the new indication.
- Period of protection starts counting on the date of the decision granting the new indication, regardless of when the original MA was granted.
- **Period of protection determined by art. 39 alone**, *i.e.* no extensions under art. 40.

7. Article 40(4) and (5)

4. Where an applicant for a marketing authorisation for a veterinary medicinal product or for a variation to the terms of a marketing authorisation submits an application in accordance with Regulation (EC) No 470/2009 for the establishment of a maximum residue limit, together with safety and residues tests and pre-clinical studies and clinical trials during the application procedure, other applicants shall not refer to results of those tests, studies and trials for a period of five years from the granting of the marketing authorisation for which they were carried out. The prohibition on using those results shall not apply, insofar as the other applicants have obtained a letter of access with regard to those tests, studies and trials.

5. If a variation to the terms of the marketing authorisation approved in accordance with Article 67 involves a change to the pharmaceutical form, administration route or dosage, which is assessed by the Agency or the competent authorities referred to in Article 66 to have demonstrated:

(a) a reduction in the antimicrobial or antiparasitic resistance; or

(b) an improvement of the benefit-risk balance of the veterinary medicinal product,

7. Article 40(4) and (5) (cont.)

- **<u>Duration of the protection period of the SMA not affected:</u>**
  - The period of protection concerns exclusively the documentation supporting the MRL, new pharmaceutical form, administration route or dosage.

- **For the period of protection under art. 40(5)** to be triggered, **confirmation by the authorities** that there is a reduction in antimicrobial/antiparasitic resistance or an improvement in B/R is required:
  - Explicit statement to be added to the public assessment report.

8. Innovation by holders of marketing authorisations granted under arts. 18 and 19

- For MAs granted under arts. 18 and 19, protection under arts 39 and 40 apply as follows:
  - ***New strength, pharmaceutical form, route of administration or target species**:*

    - Period of protection starts counting from the granting of the relevant variation/MA.

    - From that moment onwards, the concept of SMA applies (*i.e.* additional strength not entitled to protection; additional target species in accordance with art. 40).

    - "autogenerics": no additional protection – SMA applies.
  - ***New indication:***

    - Period of protection starts counting from the granting of the indication.

I.V. Lifecycle of MAs; human health and environmental aspects

1. Continuous update

- MAHs are required to update their marketing authorisations by means of a variation procedure in the following cases:
  - to ensure that the **product information** (SPC, package leaflet and labelling) is kept **up to date with current scientific knowledge;**
  - to ensure that **manufacturing methods and controls** are kept **up to date with scientific and technical progress;** and
  - submit without undue delay an application for variation - where necessary- following the assessment of **pharmacovigilance data.**

1. Continuous update (cont.)

- Holders of **marketing authorisations granted under art 18, 19 or 21** should, **where relevant**, submit variation applications swiftly **after the marketing authorisation of the reference veterinary medicinal product or of the cross-referred veterinary medicinal product is amended** to address a **safety or efficacy concern**, the risk of development of resistance or other **risks to public health, animal health or the environment <u>that is relevant</u>** to their marketing authorisations.

1. Continuous update (cont.)

- All marketing authorisation holders should consider whether **new scientific information** that becomes available in connection with **similar veterinary medicinal products authorised in the Union is relevant** in connection with their marketing authorisations and, where appropriate, take relevant measures, such as the submission of a variation application.

- Article 58(4): ***current scientific knowledge***
- Article 58(10): ***new information that may influence the assessment of B/R.***

2. ERA

- An environmental risk assessment is part of the safety information that should be provided in the marketing authorisation application.
  - For generic/hybrid and informed consent applications: an ERA may be required when the reference/cross-referred product was authorised prior to 1 October 2005.
- Environmental risks are linked to the product composition and the estimated level of exposure. **Unless duly justified** (*e.g.* different route of administration with significant impact on shedding), **information for veterinary medicinal products with similar composition should be similar**.

3. PBT/vPvB

Article 37

Decisions refusing marketing authorisations

2. A marketing authorisation shall be refused if any of the following conditions are met:

(j) the active substance within the veterinary medicinal product meets the criteria for being considered persistent, bioaccumulative and toxic or very persistent and very bioaccumulative, and the veterinary medicinal product is intended to be used in food-producing animals, unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health.

3. PBT/vPvB (cont)

- Holders of marketing authorisations granted before Article 37(2)(j) became applicable are not required to demonstrate that PBT or vPvB active substances contained in products intended for food-producing animals are essential.
- However, general obligations of MAHs include:
  - assessing the risk profile of their products in light of new evidence and **inform the competent authorities if such new information affects the benefit-risk profile** of the product; and
  - **updating their product information according to the latest scientific knowledge.**

4. Article 35 (extracts)

Article 35

Summary of the product characteristics

1. The summary of the product characteristics referred to in point (a) of Article 33(1) shall contain, in the order indicated below, the following information:

(c) clinical information:

(v) special precautions for use, including in particular special precautions for safe use in the target species, special precautions to be taken by the person administering the veterinary medicinal product to the animals and special precautions for the protection of the environment;

(xi) special restrictions for use;

(xii) special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance;

(xiii) if applicable, withdrawal periods, even if such periods are zero;

(e) pharmaceutical particulars:

(v) requirement to use take-back schemes for veterinary medicinal products for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products and, if appropriate, additional precautions regarding hazardous waste disposal of unused veterinary medicinal products or waste materials derived from the use of such products;

(k) information on the collection systems referred to in Article 117 applicable to the veterinary medicinal product concerned;

Thank you!