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## Questions and answers on describing adverse events in the product information (summary of product characteristics (SPC) and package leaflet (PL))

These questions and answers (Q&A) were developed by the Pharmacovigilance Working Party (PhVWP-V) of the Committee for Veterinary Medicinal Products (CVMP) to aid the writing or update of section 3.6 of the summary of product characteristics (SPC) and section 7 of the package leaflet (PL) to describe adverse events (AEs) of the Quality of Review Document (QRD) template (version 9).

This document aims to provide guidance for improving consistency and harmonisation for product information (PI) writing or updating, whilst it is acknowledged that a pragmatic approach should be taken to balance resource needed for this and the added value of any revised text.

The approach to alignment of the PI of authorised products with version 9 of the QRD template (QRD v9 template) may differ from the writing of the PI for initial marketing authorisation applications:

- When PI is prepared for initial marketing authorisation applications should conform to the guidance provided in the QRD v9 template and this Q&A.
- When updating existing PI for already authorised products in line with the QRD v9 template (via G.I.18 variation requiring assessment procedures) reasonable efforts should be made to apply the guidance provided in the QRD v9 template and this Q&A, however this should not require reassessing the data from the original marketing authorisation application dossier. New scientific text should not be introduced to the PIs and redundant text may be deleted. Existing information that is additional to the required text in line with the guidance given in the QRD v9 template and this Q&A, and that is relevant to the user of the medicines, may be maintained. Therefore, existing PIs may not conform entirely to the guidance provided in the QRD v9 template and the Q&A, and minor differences between PIs for similar products may remain.

First published in 2016 and not specific to QRD v9, these questions and answers were agreed with specific guidance in relation to version 9 of the QRD template for PI by the Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) and CVMP at their March 2022 meetings. Following a request from CMDv this document was revised in July 2022 to include reference to 'Undetermined' AE frequency which may be used exceptionally (see Q&As 5, 9 and 10) and to provide further clarification of Q&A 1. In March 2023 the document was further revised in the light of experience gained with updating existing PIs to bring them in line with the QRDv9 template (via a VRA G.I.18). The Q&As were revised and new Q&As (4, 7, 14 and 15) added to provide further clarity and

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examples to improve the guidance. Following a request from CMDv this document was further revised in October 2023, to provide clearer guidance when establishing frequencies when aligning PI with QRD v9, specifically when frequencies are not stated in the original PI, see Q&A 5. Further clarity has been provided in relation to the use of the tabular format to display AEs, see Q&A 11.

**1. Which adverse events (AEs) should be listed in section 3.6 of the SPC and section 7 of the package leaflet (PL)?**

Only AEs which have a potential causal association with the veterinary medicinal product (VMP) in question or same/similar VMPs, after recommended or unknown use of the product (i.e. excluding off-label use) should be listed in section 3.6 of the SPC and section 7 of the package leaflet (PL).

These AEs are reported either from spontaneous or non-spontaneous reporting systems or sources. The potential causal association is determined based on findings from data submitted with the initial marketing authorisation application or/and through analysis of pharmacovigilance data, taking into account current scientific knowledge.

Occasionally AEs resulting from off-label use of the product may be included in the PI, but not in section 3.6. of the SPC and section 7 of the PL. Other sections in the SPC and PL should be used as appropriate, e.g. section 3.10 of the SPC for AEs resulting from overdose in the target species, section 3.5 for AEs in non-target species, and the corresponding PL sections.

**2. How should AEs be described in the PI?**

AEs should be described using VeDDRA<sup>1</sup> low level terms (LLTs) where possible. VeDDRA is a comprehensive list of clinical signs (although not exhaustive) in English. It is the agreed standard terminology for AE reporting in veterinary pharmacovigilance. When clarification of VeDDRA terminology for veterinarians and animal owners is required, additional information can be annotated in footnotes under the AE table.

The use of LLTs is recommended for PIs for new marketing authorisation applications. These should be grouped by VeDDRA system organ class (SOC), where possible, but without specifying the SOC itself.

For variation procedures to update existing PIs in line with QRD v9 (VRA G.I.18), LLTs should be used whenever possible. However, there may be situations where this may not be feasible without reassessing data from the original application, for example:

- a. The authorised PI version states “gastrointestinal signs have been commonly observed”. Here, the specific LLTs are not known and therefore the table of AEs should include: “gastrointestinal signs” in the common frequency category.

Original text (QRDv8.2)	Proposed text (QRD v9)	
Gastrointestinal signs have been observed commonly	Common (1 to 10 animals / 100 animals treated):	Gastrointestinal signs

- b. The authorised PI version states: “gastrointestinal signs such as vomiting and diarrhoea have been commonly observed”. Here, because of the words “such as”, it is unclear what the other gastrointestinal effects are, and therefore the table of Aes should include: “gastrointestinal signs (e.g. vomiting, diarrhoea) in the common frequency category.

<sup>1</sup> [Veterinary Dictionary for Drug Regulatory Activities](#); Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products (EMA/CVMP/PhVWP/10418/2009) and Guidance notes on the use of VeDDRA (EMA/CVMP/PhVWP/288284/2007).

Original text (QRDv8.2)	Proposed text (QRD v9)	
Gastrointestinal signs such as vomiting or diarrhoea have been observed commonly	Common (1 to 10 animals / 100 animals treated):	Gastrointestinal signs (e.g. vomiting or diarrhoea)

VeDDRA LLTs that contain the abbreviation “NOS” (Not otherwise specified) should be stated in the SPC and PL with the abbreviation removed, i.e., “Appetite disorder NOS” should be stated as “Appetite disorder”.

See also Question 4 Can the wording of the AE used in the summary of product characteristics (SPC) be different to that of the package leaflet (PL)?

### 3. What if there is no appropriate VeDDRA LLT available to describe the AE?

When the AE is not already available as a VeDDRA LLT, an appropriate alternative VeDDRA LLT should be selected that most closely reflects the AE.

If there is no appropriate alternative VeDDRA LLT in the current VeDDRA list, a proposal for a new LLT should be made to the VeDDRA subgroup. The proposed VeDDRA LLT should be added to the proposed PI.

It is preferable that appropriate VeDDRA LLTs exists for all listed AEs to enable standardised and harmonised reporting of AEs within the Union.

The process for submission of proposals for new VeDDRA terms is outlined in the permanent [‘VeDDRA Call for comments’ published on the EMA website \(see Call for comments on the Veterinary Dictionary for Drug Regulatory Activities \(VeDDRA\) standard list for EudraVigilance Veterinary \(EVVet\)\)](#) a reference to the specific PI where the new VeDDRA LLT is used should be added in the ‘Comments’ column of the template for requesting new terms or revision of VeDDRA terms.

### 4. Can the wording of the AE used in the summary of product characteristics (SPC) be different to that of the package leaflet (PL)?

The terminology in the SPC and PL may differ. The PL should be written in terms that are understandable to the general public (as stated in Article 14(3) of Regulation (EU) 2019/6), i.e. plain language or ‘layman’s terms’. Although most VeDDRA LLTs are generally comprehensible to the general public, there may be some cases where there is no appropriate, easily understandable VeDDRA LLT describing the AE in the SPC. In such cases, it is recommended to propose a new VeDDRA LLT to the VeDDRA subgroup as described in Q&A 3. The VeDDRA LLT from the SPC may be included in the PL followed by the layman’s term equivalent in parentheses:

e.g. “Ataxia (Incoordination)”.

When aligning existing PI with QRD v9 it may be generally acceptable to maintain the authorised text (see also question 2).

### 5. UPDATED: How should the frequency of AEs be expressed?

The frequency of AEs should be described using the categories described in the QRD template and ranked so that the most frequently occurring clinical signs are listed first. Five standard frequency categories have been retained to maintain international harmonisation and to minimise confusion when comparing frequencies of AEs in PIs worldwide. In addition, a further frequency category has

been introduced, for exceptional use only. The category is 'Undetermined frequency (cannot be estimated from the available data)' and it is necessary to facilitate the adaptation of older PIs to the QRD v9 template, see details below.

In each frequency category, AEs should be grouped in accordance with their VeDDRA system organ classes (SOC). In the examples below, LLTs are grouped under the SOC: Application site disorders and the SOC: Digestive tract disorders:

e.g. Application site alopecia, Application site lesion;  
Vomiting, Gastric ulcer, Haematemesis.

Some VeDDRA LLTs in the [VeDDRA standard list](#) have associated text in parentheses providing VeDDRA coding guidance. This text should not be included in the PI e.g. 'Abnormal vision (see also impaired vision)' should be stated as 'Abnormal vision' in the PI.

When updating PI from QRD v8.2 to QRD v9, in the first instance, the frequency categories for each AE should not be changed. When frequencies are not stated in the original PI (i.e. QRD v8.2 format), typically when updating older PIs where the frequency categories have not been used (e.g. 'vomiting occurs sometimes') the 'new/appropriate' frequencies should be calculated, and justified, from the data on which the original PI statements were based (e.g. pre-authorisation studies and/or pharmacovigilance data (e.g. periodic safety update reports (PSURs)) or, if this data is not available, cumulative pharmacovigilance data (from the initial marketing authorisation data to present) from the Union Pharmacovigilance Database). Justification for the proposed frequency should be provided e.g. by including the incidence calculation used to determine the chosen frequency or another suitable reason. These frequencies should be accepted without the request of additional data (e.g. no request for additional VRAs to assess data). Only when frequencies cannot be determined from any of these data sources (e.g. pre-authorisation studies or cumulative pharmacovigilance data) may the category 'undetermined frequency' be used, however this should be **exceptional**. When 'undetermined frequency' has been used, as soon as it becomes possible to define a frequency, for example using the data sources described above, the AE should be moved to the appropriate frequency category (see question 9).

## 6. Which frequencies should be published on the PI?

AEs that are observed in pre-authorisation studies (e.g. safety and/or efficacy studies) or post-authorisation (reported through the pharmacovigilance system) which have a potential causal association with the VMP should be included in the PI.

For AEs that are observed both pre-authorisation and post-authorisation, the highest frequency observed should be used in the PI.

## 7. NEW: Can the AE frequencies published in the PI be different to the AE reporting frequencies from other sources e.g. ADR reporting website?

Yes. The PI reflects AE frequencies observed in supporting studies at the time of granting of the initial marketing authorisation or known at the time of approvals of subsequent post-authorisation procedures (e.g. reported through the pharmacovigilance system). The PI is not continuously updated to reflect actual AE reporting frequencies. Therefore, the AE reporting frequencies in the PI may differ from those available on the [European database of suspected adverse drug reaction reports \(adrreports.eu\)](#), which reflects the frequency of AEs reported to the EU database on a continuous basis. A statement can be found on the [ADR reporting website](#) which addresses this and explains to the user that the frequencies seen in the ADR database may differ from those stated in the SPC.

## **8. Why is there no longer a distinction made between AE frequencies arising from controlled studies and those from spontaneous reporting?**

The data source (controlled studies versus spontaneous reporting) of the AE is not considered useful information that can improve the safety or efficacy of a VMP. The requirement to indicate the data source was removed with revision of the QRD template to version 9 to enable AE information to be presented more clearly and simply for the benefit of users of VMPs. When updating existing PIs to QRD v9 via VRA G.I.18 the source of the data should be deleted.

## **9. Can I update the PI to change the frequency of AEs?**

Yes, the frequency of AEs may be updated in the PI. If post-authorisation experience indicates reporting of an AE at a higher frequency than that observed in pre-authorisation studies and described in the PI, it is strongly recommended to revise the frequency of that AE in the PI to reflect the observed higher frequency. Revision of PIs to reflect lower frequencies of AEs ('downgrading') is generally not permitted unless substantiated by appropriate scientific data from controlled studies.

When an AE has been put into the frequency category 'Undetermined frequency (cannot be estimated from the available data)' (see questions 5 and 10), it is expected that the MAH updates the frequency as soon as one can be defined.

## **10. What are the requirements related to AEs and AE frequencies for reference products and generics and informed consent products?**

For initial authorisation of a generic or informed consent product, the AEs and frequency of AEs in the PI of the reference medicinal product apply exactly, i.e., 'copy and paste'. Where no frequency is expressed for a certain AE in the PI of the reference product, this AE can be included in the additional frequency category called 'Undetermined frequency (cannot be estimated from the available data)' in a row at the end of the table (see question 5).

Post-marketing experience should be reflected in a consistent manner, so that when the PI of a reference product is updated with new information on active-substance related AEs, that of the generic or informed consent product should also be updated and, potentially, vice-versa, through an appropriate regulatory procedure. Other AEs, possibly arising from differences in excipient composition of the generic or informed consent product compared to the reference product, may be added to, but not replace, AEs on the product information, unless appropriate supporting data have been provided.

## **11. UPDATED: Is it a requirement to use a table to list AEs in the PI?**

For section 3.6 of the SPC, it is a requirement to tabulate AEs. Tables present AEs in a clear and simple format and improve readability for product users.

The template includes approaches for further simplifying the tabular presentation of AE information, e.g., presenting tables by animal species, using annotations in footnotes and deleting unused frequency rows.

For section 7 of the PL, there are three options for the presentation of AEs:

1. The same presentation as in the SPC, e.g. a two-column table;
2. A single column; or
3. Text only – which should be in sections maintaining the headings and structure used in the SPC and described as follows:

Very common (> 1 animal / 10 animals treated):

Vomiting

Common (1 to 10 animals / 100 animals treated):

Diarrhoea

It is appreciated that there are practical constraints with lack of space and narrow line width when generating readable PLs. Irrespective of the format used, the information and sequence of information given in section 3.6 of the SPC should be maintained in section 7 of the PL.

Generally, AEs should be presented in a tabular format for each target species. However, it is permitted to collate AEs related to several target species in a single table if the AEs are strictly the same or when there are a few AEs which have a different frequency, the lower frequency can be annotated in a footnote immediately below the table. It is essential that AEs for a single target species are contained within the same table and not distributed across multiple tables. It is important to consider the clarity and readability of section 3.6 in SPC and section 7 in PL when implementing the tabular format.

## **12. How should additional information related to AEs be presented in the PI?**

Additional information relating to AEs should be kept to a minimum and should be relevant for the VMP user and prescriber. The use of footnotes under the AE table to annotate information is **preferred** to provide a clearer and cleaner tabulated list of AEs. Superscript text/symbols should be used after the AE and before the related footnote. It is also permitted to place very brief additional information in parentheses after the relevant VeDDRA LLTs, but care should be taken to not affect the readability of the table. The number of words in parentheses should be limited.

## **13. What comprises additional information for listed AEs in the PI?**

The use of additional information should be restricted to information that supports AE management or improves understanding of use of the VMP. Undefined or imprecise statements on duration, severity and outcome of the AEs should be avoided unless useful to aid the decision-making of the prescriber or VMP user.

Additional information on specific clinical signs should be preferably added beneath the table of listed AEs as a footnote. Examples of permitted additional information:

- advice on whether or at what point to consult a veterinarian;
- specific measures to be taken – or to be avoided - by the animal owner or by the veterinarian, i.e., administration of an antidote, removing of a collar, washing of an application site;
- advice on the nature of the observed AEs e.g. mention that vomiting will occur at the beginning of the treatment and will resolve as the treatment continues (e.g., cabergoline in dogs);
- expected severity, duration and any other information providing further description of clinical signs, derived from the analysis of AE reports. Preferably this should be precise and factual and where possible, numeric values should be used e.g. lameness (1-3 weeks following booster vaccination), vomiting (generally lasting 2 days), injection site oedema (up to 10 cm).
- when existing PIs are aligned with the QRD v9 template, it is permitted to retain imprecise statements which are already in the original PI. It is preferable to include these statements as footnotes. Such imprecise statements can include wording such as 'of short duration', 'transient', 'temporary', 'self-limiting' and 'resolves spontaneously'.

- the wording of the PI should clarify when an LLT may be associated with several kinds of AEs and pathophysiological mechanisms, e.g., diarrhoea should be clearly associated either with anaphylaxis or to an enterokinetic action of an active substance or both, if reported for both types of AEs.

Examples of additional information that should be avoided when PI is prepared for initial marketing authorisation applications include the following:

- imprecise statements such as 'of short duration', 'transient', 'temporary', and statements on the outcomes of clinical signs: 'self-limiting' or 'spontaneous resolution', statements on frequency of AEs: 'occasionally', 'sometimes', 'in most cases'.

#### **14. What standard text should be used in Section 3.6 Adverse events of the SPC to cross-refer to the package leaflet (PL) section for contact details for reporting adverse events?**

In section 3.6 of the SPC, there is standard text cross-referencing to the PL section 16 for contact details to report suspected AEs to either the MAH or local representative, as follows:

- See also **section 16** of the package leaflet for respective contact details.

Not all printed PLs contain numbered sections. Therefore, the following alternative standard phrase should be used at the end of SPC section 3.6 until the discrepancy in the published QRD v9 template is corrected:

- See the package leaflet for respective contact details.

#### **15. Should pictograms relating to special warnings or contraindications in existing PI be maintained when aligning with QRD v9 template\*?**

Pictograms relating to special warnings or contraindications that have already been approved, should be maintained when aligning the PI with QRD v9 template e.g. warnings against use of permethrin-containing products in cats (which can be fatal).

Ordinarily pictograms may be included in the PL or on the labelling (immediate packaging or outer packaging) if requested by the applicant and if in line with the QRD guidance on the use of approved pictograms ([EMA/776723/2017 rev. 2](#)).

\* The information provided in answer to this question is without prejudice to the provisions in the implementing act foreseen by Article 17(3) of Regulation (EU) 2019/6 providing a list of the abbreviations and pictograms common through the Union to be used for the purposes of Articles 10(2) and 11(3) of Regulation (EU) 2019/6.

## **References**

- [European Medicines Agency \(2021\) Quality Review of Documents veterinary product-information annotated template \(English\) version 9](#)
- [Committee for Medicinal Products for Veterinary Use \(CVMP\) \(2021\) Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products \(EMA/CVMP/PhVWP/10418/2009\)](#)
- [Committee for Medicinal Products for Veterinary Use \(CVMP\) \(2021\) Guidance notes on the use of VeDDRA \(EMA/CVMP/PhVWP/288284/2007\)](#)