EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Standard operating procedure

| Title: Management of pharmacovigilance Rapid Alerts (RAs) and Non Urgent Information (NUI) for medicinal products for veterinary use | | |
|---|---|---|
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## 1. Purpose

To manage, with the appropriate degree of urgency, pharmacovigilance Rapid Alerts (RAs) and Non Urgent Information (NUI) for medicinal products for veterinary use, circulated by Member States (MSs), EFTA countries, the Agency or the European Commission, about newly available pharmacovigilance data for veterinary medicinal products which indicate that urgent action could be needed to protect animal or public health or which are circulated for collection and exchange of information within the EU Regulatory Network.

## 2. Scope

This SOP applies to staff in the Veterinary Medicines sector, CVMP members and CVMP Pharmacovigilance Working Party members.

## 3. Responsibilities

It is the responsibility of the Head of Veterinary Medicines to ensure that this procedure is adhered to. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 9.

## 4. Changes since last revision

The SOP has been reviewed to update the references and capture minor procedural changes.

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## 5. Documents needed for this SOP

- *Template for Rapid Alert and Non Urgent Information in Pharmacovigilance – Initial*
  Annexes of Volume 9B of The rules governing medicinal products in the European Union, October 2011 (http://ec.europa.eu/health/files/eudralex/vol-9/vol_9b_2011-10.pdf); Word version.
- *Template for Rapid Alert and Non Urgent Information in Pharmacovigilance – response*
  Annexes of Volume 9B of The rules governing medicinal products in the European Union, October 2011 (http://ec.europa.eu/health/files/eudralex/vol-9/vol_9b_2011-10.pdf); Word version.
- Model letter: RA - 01 information request letter (in Siamed);
- Rapid alert assessment report template - *under development*

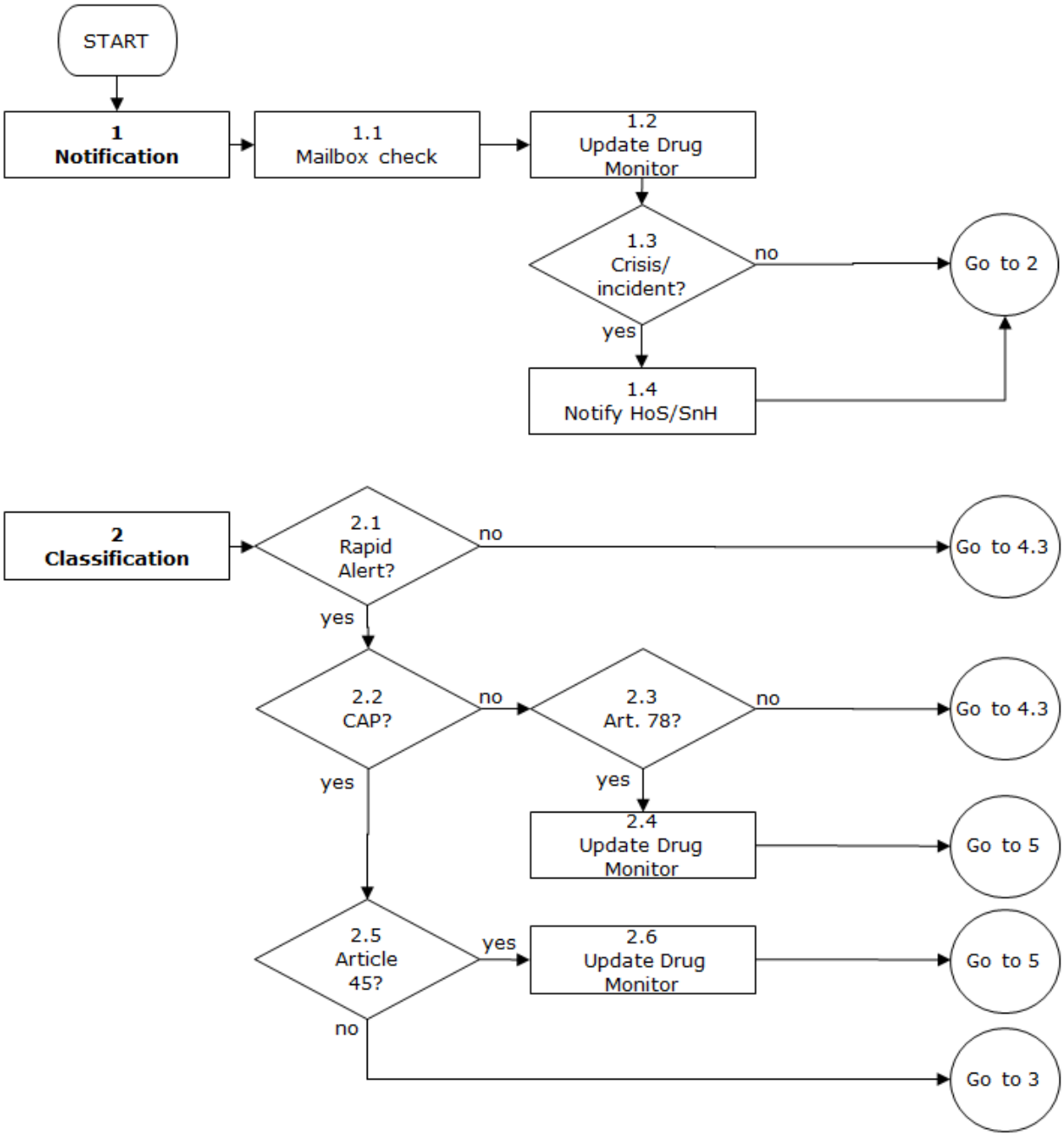
## 6. Related documents

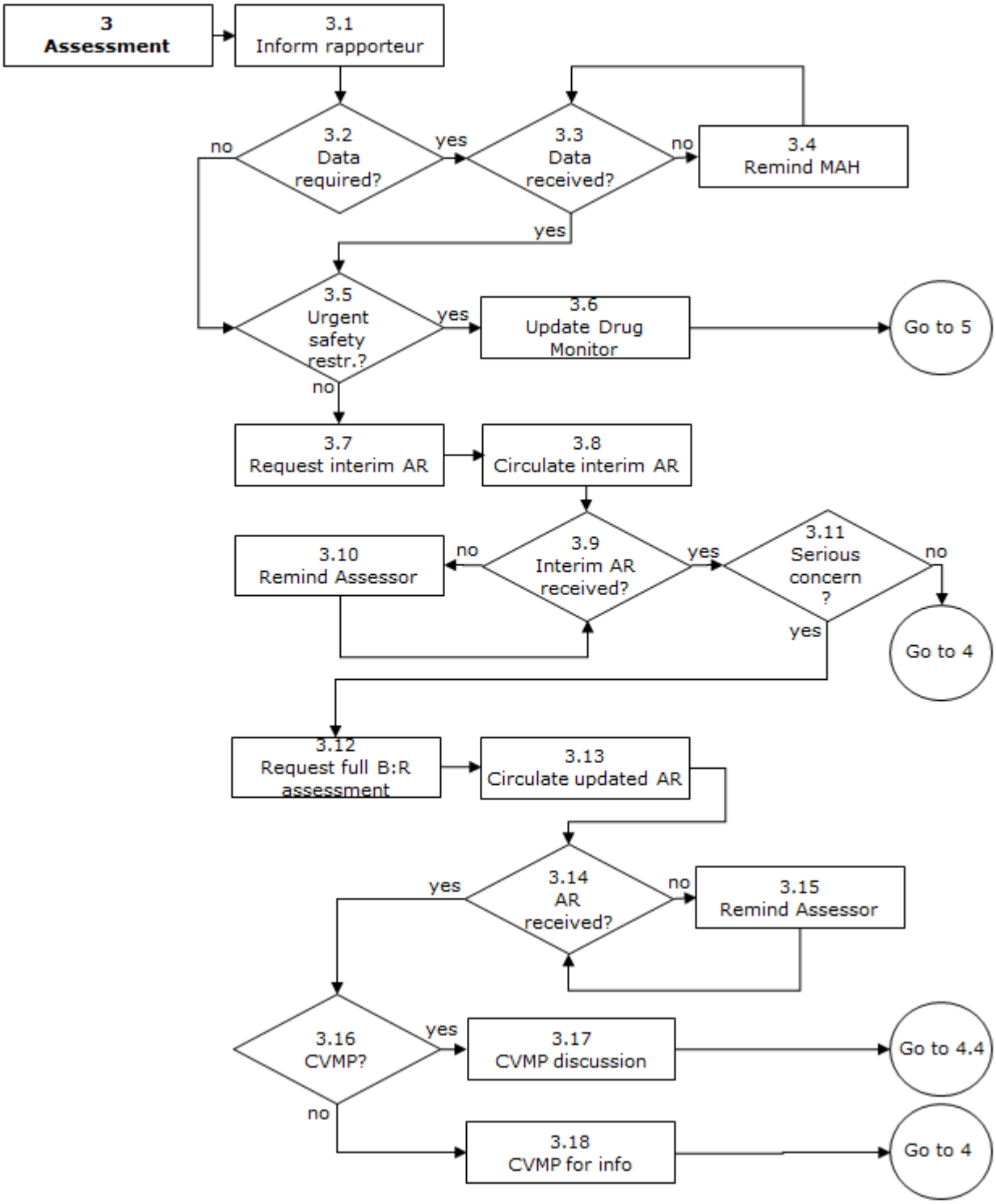
- Drug Monitor (CVMP/060/00);
- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products;
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;
- Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products;
- Volume 9B of The rules governing medicinal products in the European Union, October 2011
- CVMP Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/07);
- SOP/V/4025 on Procedures in accordance with Article 78 of Directive 2001/82/EC related to pharmacovigilance measures for veterinary medicinal products authorised in the European Union;
- Incident management plan for medicines for veterinary use (EMA/711053/2010);
- SOP/V/4003 on the Procedure to be followed when the incident management plan for medicines for veterinary use is triggered.
- SOP/PDM/1004 on Core Master Files of medicinal products for human and veterinary use following the centralised procedure

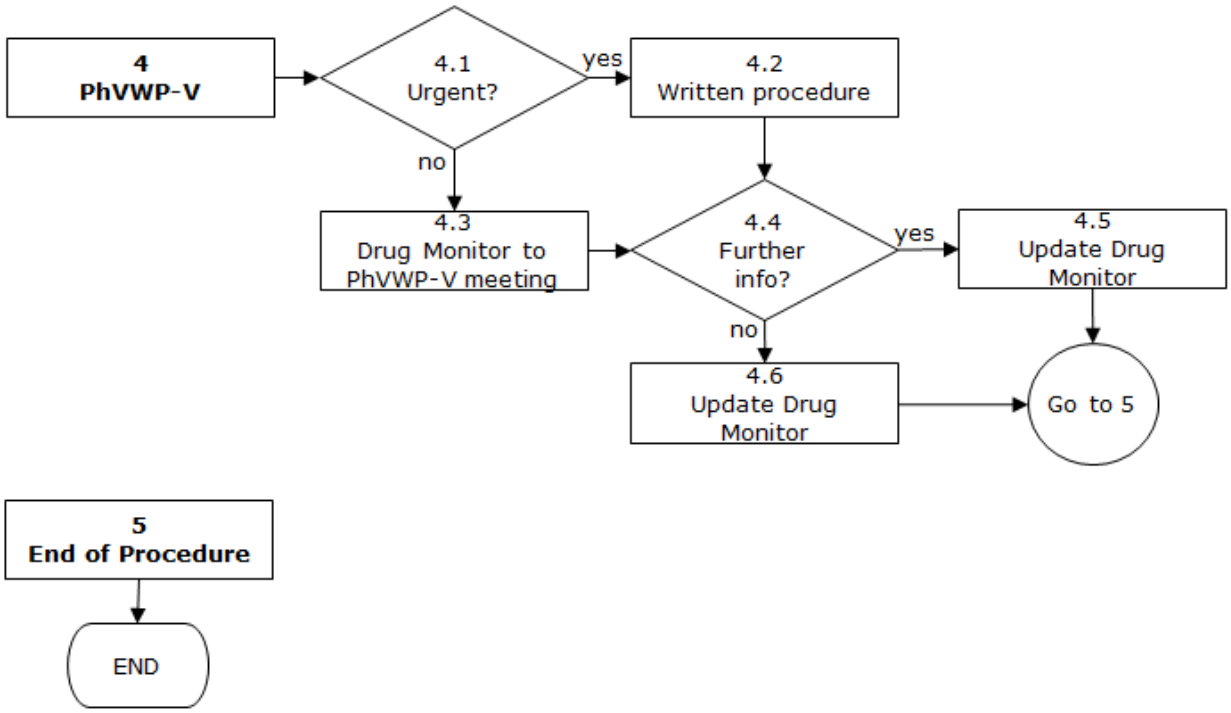
# 7. Definitions

| | |
|---|---|
| Art 22 Procedure | Procedure under Article 22 of Commission Regulation No 1234/2008, concerning urgent safety restrictions |
| Art 45 Procedure | Procedure under Article 45(4) of Regulation 726/2004 of the European Parliament and of the Council, concerning urgent safety measures taken by a Member State, including suspension |
| Art 47 Procedure | Procedure under Article 47 of Regulation 726/2004 of the European Parliament and of the Council, concerning CVMP opinions on measures necessary following receipt of suspected adverse reaction reports |
| Art 78 Procedure | Procedure under Article 78 of Directive 2001/82/EC of the European Parliament and of the Council, concerning urgent pharmacovigilance measures considered or taken by Member States |
| AA | Administrative assistant at EMA (here: VROS section) |
| APH | Animal and Public Health section in the Veterinary Medicines sector |
| AST | Assistant at EMA (assigned to veterinary pharmacovigilance activities) |
| cMF | Core master file |
| CVMP | Committee for Medicinal Products for Veterinary Use |
| DEM | Development and Evaluation of Medicines section in the Veterinary Medicines sector |
| DREAM | Document Records Electronic Archive Management |
| HoS | Head of Sector (here: Head of Veterinary Medicines) |
| MA | Marketing authorisation |
| MAH | Marketing authorisation holder |
| MS | Member State of the European Union (EU/EEA) |
| NCA | National competent authority |
| NUI | Non Urgent Information |
| Originator | Party initiating RA/NUI |
| PhV | Pharmacovigilance (here: veterinary) |
| PhV SA | Scientific administrator for veterinary pharmacovigilance (here PhV SA responsible for rapid alerts and non-urgent information) |
| PhVWP-V | CVMP Pharmacovigilance Working Party |
| PM | Project Manager (here: product responsible PM in APH or DEM section) |
| RA | Rapid Alert |
| Rapporteur | Rapporteur for centrally authorised product |
| SnH | Section head (here: Head of Animal and Public Health) |
| VROS | Veterinary Regulatory and Organisational Support section in the Veterinary Medicines sector |

## 8. Process map(s)/ flow chart(s)




3
Assessment
3.1
Inform rapporteur
3.2
Data
required?
no
yes
3.3
Data
received?
no
3.4
Remind MAH
yes
3.5
Urgent
safety
restr.?
yes
3.6
Update Drug
Monitor
Go to 5
no
3.7
Request interim AR
3.8
Circulate interim AR
3.10
Remind Assessor
no
3.9
Interim AR
received?
yes
3.11
Serious
concern
?
no
yes
Go to 4
3.12
Request full B:R
assessment
3.13
Circulate updated AR
yes
3.14
AR
received?
no
3.15
Remind Assessor
3.16
CVMP?
yes
3.17
CVMP discussion
Go to 4.4
no
3.18
CVMP for info
Go to 4


4
PhVWP-V
4.1
Urgent?
yes
4.2
Written procedure
no
4.3
Drug Monitor to
PhVWP-V meeting
4.4
Further
info?
yes
4.5
Update Drug
Monitor
no
4.6
Update Drug
Monitor
Go to 5


5
End of Procedure
END

# 9. Procedure

| Step | Action | Responsibility |
|---|---|---|
| **1.0** | **Receipt of RA or NUI notification** | |
| 1.1 | Check Veterinary RA and Veterinary Pharmacovigilance EudraNet mailboxes for RA and NUI notifications: | |
| | • Daily: Check EMA-V.RA mailbox for RA (or responses to RA). If RA is received, forward to AST for saving in DREAM. If NUI has been circulated to EMA-V.RA mailbox, forward message (including any attachments) to EudraNet address LIST-V-PHARMACOVIGILANCE@EUDRA.ORG. | PhV SA |
| | • 2-3 times a week: Check EMA-V.Pharmacovigilance for NUI (or responses to NUI). If NUI is received, save it in DREAM and forward the locator to PhV SA. | AST |
| 1.2 | Update Drug Monitor in DREAM: | PhV SA |
| | • Update date in relevant field; | |
| | • Create new topic; insert data in all fields as far as it is known – otherwise state "unknown"; | |
| | • *Action taken/Outcome*: If regulatory measures (suspension, withdrawal, amendment of product literature, or other regulatory measure) have been taken, indicate the MS and the action taken clearly. If the new RA is related to quality defect only, then include information that this RA is to be considered as a product (quality) defect and will be closed after the PhVWP-V meeting in [insert month and year of next PhVWP-V meeting]; | |
| | • *Action taken by whom*: Indicate acting MS (originator of RA/NUI should always be included); | |
| | • *Status:* Indicate if RA/NUI is ongoing or closed. | |
| 1.3 | Does the notification fulfil the criteria of an incident or crisis in accordance with the incident management plan for medicines for veterinary use or has advice been requested from the incident review group?<br>If **yes**, go to 1.4<br>If **no**, go to 2.0 | |
| 1.4 | Notify HoS/SnH in accordance with *SOP/V/4003* on the Procedure to be followed when the incident management plan for medicines for veterinary use is triggered.<br>Proceed to 2.0 | PhV SA |
| **2.0** | **Classification of the RA/NUI** | |
| 2.1 | Is the notification a PhV-related rapid alert?<br>If **yes**, go to 2.2<br>If **no** (NUI or product (quality) defect related RA), go to 4.3 | PhV SA |
| 2.2 | Is the notification about a centrally authorised product?<br>If **yes**, go to 2.5<br>If **no**, go to 2.3 | PhV SA |

| Step | Action | Responsibility |
|---|---|---|
| 2.3 | Has the MA been suspended or is the NCA that sent the notification considering suspension or withdrawal of the MA or variations to the MA in accordance with Article 78?<br><br>If **yes**, go to 2.4<br>If **no**, go to 4.3 | PhV SA |
| 2.4 | Update Drug Monitor, especially:<br><br>• *Action taken / Outcome*: Insert "processed under Art. 78 procedure".<br><br>• *Status:* Close RA/NUI.<br><br>Liaise with PhVWP-V secretariat to include as a new point under "Rapid Alerts" on the agenda for the next PhVWP-V meeting, informing on diversion of procedure to Article 78 procedure.<br><br>Notify HoS/SnH and follow Article 78 procedure according to *SOP/V/4025*.<br><br>Proceed to 5.0 | PhV SA |
| 2.5 | Does the notification fulfill the criteria for a procedure under Article 45(4) of Regulation 726/2004 concerning urgent action?<br><br>If **yes**, go to 2.6<br>If **no**, go to 3.0 | PhV SA |
| 2.6 | Update Drug Monitor, especially:<br><br>• *Action taken / Outcome*: Insert "processed under Art. 45(4) procedure (urgent safety measures)".<br><br>• *Status:* Close RA/NUI.<br><br>Liaise with PhVWP-V secretariat to include as a new point under "Rapid Alerts" on the agenda for the next PhVWP-V meeting, informing on diversion of procedure to Article 45(4) procedure.<br><br>Inform HoS, SnH and DEM and/or VROS PMs (as advised by HoS/SnH).<br><br>Proceed to 5.0 and follow *Article 45(4) procedure*. | PhV SA<br><br>PhV SA<br><br>PhV SA |
| **3.0** | **Assessing the rapid alert** | |
| 3.1 | Inform rapporteur and DEM PM. In consultation with rapporteur and originator, determine who will prepare the assessment of the RA. | PhV SA |
| 3.2 | In liaison with rapporteur/originator prepare communication to MAH, including deadline for response or submission of data, if applicable. Forward letter to HoS/SnH for review, and HoU if needed, in conjunction with DEM PM and legal services as appropriate.<br><br>Send communication to MAH.<br><br>Is a response or data expected from MAH?<br><br>If **yes**, go to 3.3<br>If **no**, go to 3.5 | PhV SA<br><br>AST |
| 3.3 | Has data/response been received from MAH by deadline?<br><br>If **yes**, go to 3.5<br>If **no**, go to 3.4 | PhV SA/AST |

| Step | Action | Responsibility |
|---|---|---|
| 3.4 | Send reminder to MAH (with new short-term deadline) for response or submission of data.<br><br>Go to 3.3 | PhV SA/AST |
| 3.5 | Is the MAH initiating an urgent safety restriction?<br><br>If **yes**, go to 3.6<br>If **no**, go to 3.7 | PhV SA |
| 3.6 | Update Drug Monitor, especially:<br><br>• *Action taken / Outcome*: Insert "processed under Art. 22 procedure (urgent safety restrictions)".<br><br>• *Status:* Close RA/NUI.<br><br>Liaise with PhVWP-V secretariat to include as a new point under "Rapid Alerts" on the agenda for the next PhVWP-V meeting, informing on diversion of procedure to Article 22 procedure.<br><br>Inform DEM PM.<br><br>Proceed to 5.0 and follow *Article 22 procedure*. | PhV SA |
| 3.7 | Forward available data/response to rapporteur/originator, requesting interim assessment report (including benefit-risk evaluation) to be circulated to LIST-V-RA@EUDRA.ORG within a specified deadline (usually within 5 weeks). | PhV SA |
| 3.8 | Circulate assessment report to LIST-V-RA@EUDRA.ORG by specified deadline | Rapporteur/ originator |
| 3.9 | On deadline: has assessment report been sent to Veterinary RA Eudranet mailbox?<br><br>If **yes**, go to 3.11<br>If **no**, go to 3.10 | PhV SA |
| 3.10 | Send reminder to rapporteur/originator (with new short-term deadline) for submission of interim assessment report via Eudranet.<br><br>Go to 3.9 | PhV SA |
| 3.11 | Has the rapporteur/originator identified a serious risk to public or animal health in the interim assessment report?<br><br>If **yes**, go to 3.12<br>If **no**, go to 4.0 | PhV SA |
| 3.12 | Request rapporteur/originator to update assessment report, including a full benefit-risk evaluation and circulate to LIST-V-RA@EUDRA.ORG within a specified deadline. | PhV SA |
| 3.13 | Circulate updated assessment report, including full benefit-risk evaluation, to LIST-V-RA@EUDRA.ORG by deadline | Rapporteur/ originator |
| 3.14 | Has updated assessment report, including full benefit-risk evaluation, been sent to Veterinary RA EudraNet mailbox by deadline?<br><br>If **yes**, go to 3.16<br>If **no**, go to 3.15 | PhV SA/AST |

| Step | Action | Responsibility |
|---|---|---|
| 3.15 | Send reminder to rapporteur/originator (with new short-term deadline) for submission of updated assessment report, including full benefit-risk evaluation, via Eudranet.<br><br>Go to 3.14 | PhV SA/AST |
| 3.16 | Has the rapporteur/originator identified a need to circulate the assessment report, including full benefit-risk evaluation, to CVMP for consideration or decision?<br><br>If **yes**, go to 3.17<br>If **no**, go to 3.18 | PhV SA |
| 3.17 | Send the assessment report, including full benefit-risk evaluation, to the CVMP for consideration and decision at its next meeting.<br><br>Go to 4.4 | PhV SA |
| 3.18 | Circulate assessment report for information at next CVMP meeting.<br><br>Proceed to 4.0 | PhV SA |
| **4.0** | **Consideration by PhVWP-V** | |
| 4.1 | Does the assessment report consider the matter urgent[1]?<br><br>If **yes**, go to 4.2<br>If **no**, go to 4.3 | PhV SA |
| 4.2 | In liaison with rapporteur/originator and PhVWP-V secretariat, circulate the interim or updated assessment report (as appropriate) to the PhVWP-V (via LIST-V-RA@EUDRA.ORG) for consideration by written procedure with request for appropriate action.<br><br>Go to 4.4 | PhV SA |
| 4.3 | In liaison with PhVWP-V secretariat, include Drug Monitor in 1st mailing for PhVWP-V (update in 2nd, if applicable).<br><br>For each *ongoing* RA/NUI:<br>• Include topic as separate point on agenda.<br>• Include original RA/NUI (and assessment report for consideration and conclusion, if applicable) under relevant point<br>• Include responses only where MS(s) consider actions[2], to facilitate the discussion. | PhV SA |
| 4.4 | Outcome of written procedure or discussions at PhVWP-V or CVMP: Is further information required from the MAH?<br><br>If **yes**, go to 4.5<br>If **no**, go to 4.6 | PhV SA |

[1] The rapporteur is to decide on urgency/non-urgency for consideration of the issue. To avoid any doubt, this should be indicated and justified in the assessment report by the rapporteur. The rapporteur also needs to clearly define the action to be requested from the PhVWP-V, and to clearly define any question to be addressed by the PhVWP-V.

[2] Since RA/NUIs are circulated through EudraNet mailboxes, all PhVWP-V members have access through the national EudraNet mailboxes to the full responses.

| Step | Action | Responsibility |
|---|---|---|
| 4.5 | Inform MAH.<br>Update Drug Monitor, especially:<br>• *Action taken / Outcome*: Insert "processed under Art. 47 procedure (CVMP opinion)".<br>• *Status:* Close RA/NUI.<br>Inform DEM PM.<br>Proceed to 5.0 and follow *Article 47 procedure*. | PhV SA |
| 4.6 | Update Drug Monitor, especially:<br>• *Action taken / Outcome*: Include major items of discussion, if necessary, in the form of: "*<PhVWP-V/CVMP><insert month of meeting>: <insert brief conclusion of discussion>*<br>• *Status:* Close RA/NUIs that have been closed during CVMP or PhVWP-V meeting, pay special attention to product defect RAs that are normally closed after one meeting.<br>Circulate assessment report to CVMP for information at next meeting (if not already done).<br>Proceed to 5.0 | PhV SA |
| **5.0** | **End of procedure** | |

# 10. Records

Archiving of RA and NUI in DREAM:

- Product defect related RA: *Cabinets/03. Pharmacovigilance/PhV - Veterinary/Surveillance/Rapid Alerts-NUIS/Product defect related RA-NUIS (non-phv)* (not applicable to pharmacovigilance)
- PhV-related RA: for new topics, create new folder in *Cabinets/03. Pharmacovigilance/PhV - Veterinary/Surveillance/Rapid Alerts-NUIS/1 Rapid Alerts* in the form of "YYYY (chronological nr) – Topic (Product) Name – Initiating MS", then save message as "Topic (Product) Name - RA initial– MS - date of receipt". Save all further correspondence related to this topic in the same folder. Responses to be saved in the form of "Topic (Product) Name – RA response– MS - date of receipt".
- NUI: for new topics, create new folder in *Cabinets/03. Pharmacovigilance/PhV - Veterinary/Surveillance/Rapid Alerts-NUIS/2 NUIS* in the form of "YYYY (chronological nr) – Topic (Product) Name – Initiating MS", then save message as "Topic (Product) Name - NUI initial– MS - date of receipt". Save all further correspondence related to this topic in the same folder. Responses to be saved in the form of "Topic (Product) Name - NUI response– MS - date of receipt".

In general, attachments are saved separately in the same folder and in the same form.