EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Referral procedures in accordance with the provisions of Articles 33(4), 34 and 35 of Directive 2001/82/EC, and Article 13 of Commission Regulation (EC) No 1234/2008, related to veterinary medicinal products authorised in the European Union		
Status: **PUBLIC**		Document no.: SOP/V/4024
Lead author	Approver	Effective date: 18-DEC-15
Name: Beyhan Mustafov	Name: David Mackay	Review date: 18-DEC-18
Signature: on file	Signature: on file	Supersedes: SOP/V/4014 (14-DEC-12) SOP/V/4024 (23-APR-12)
Date: 17-DEC-15	Date: 17-DEC-15	TrackWise record no.: 4619

1. Purpose

To describe the procedure for referrals related to veterinary medicinal product(s) (VMPs) submitted to the CVMP by a Member State, the European Commission or the applicant/marketing authorisation holder, including the procedure for re-examination of CVMP opinions on referrals upon request of the applicant/marketing authorisation holder in accordance with the provisions of Article 36(4) of Directive 2001/82/EC.

The procedure does not apply for procedures in accordance with Article 78 of Directive 2001/82/EC, related to pharmacovigilance measures for veterinary medicinal products authorised in the European Union.

The procedure does not describe steps to be taken by the Member States prior to notification, nor steps taken by the European Commission post opinion.

2. Scope

This SOP describes the procedure for referrals notified to the CVMP under Article 33(4), Article 34 and Article 35 of Directive 2001/82/EC, and under Article 13 of Commission Regulation (EC) No 1234/2008.

A referral procedure to the CVMP can be initiated on the basis of the following articles of the EU pharmaceutical legislation:

- **Article 33(4) of Directive 2001/82/EC**: When Member States fail to reach an agreement on an application for a marketing authorisation of a VMP within the framework of the mutual recognition or decentralised procedures;

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- **Article 34 of Directive 2001/82/EC**: When Member States adopt divergent decisions concerning the authorisation of a VMP, suspension or revocation of authorisation of that product, following submission of two or more national applications;
- **Article 35 of Directive 2001/82/EC**: Where the interests of the Union are involved[1], and before reaching a decision on the suspension or withdrawal of an authorisation or on a variation to the terms of a marketing authorisation, with regard to any VMP regardless of the marketing authorisation procedure followed. If considered necessary in order to protect public or animal health, other VMPs containing an active substance of the same therapeutic class may also be referred, where a class effect is the subject of this procedure;
- **Article 13 of Commission Regulation (EC) No 1234/2008**: When Member States fail to reach an agreement on a Type II variation to the terms of marketing authorisation of a VMP.

This SOP applies to the European Medicines Agency (EMA) staff in the Veterinary Medicines Division.

3. Responsibilities

It is the responsibility of the Head of Veterinary Medicines Department 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 in *section 9*.

4. Changes since last revision

New templates have been applied and the procedure has been revised to include referral procedures under Article 33(4) of Directive 2001/82/EC and under Article 13 of Commission Regulation (EC) No 1234/2008.

5. Documents needed for this SOP

Models are available under X:\Templates\Others\Vet\Referrals.

6. Related documents

- 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, as amended;
- 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;
- 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 use and veterinary use and establishing a European Medicines Agency;
- The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 6A, Chapter 3
- Checklist on post opinion phase following CVMP opinions on procedures under Articles 33(4), 34, 35 and 78 of Directive 2001/82/EC, as well as Article 13 of Commission Regulation (EC) No 1234/2008;
- Questions and answers on referrals procedures for veterinary medicinal products;

[1] "**Union interest**" refers to the interest of animal or public health or the environment related to a veterinary medicinal product which is on the market in the European Union, in the light of new data relating to quality, safety, efficacy or new pharmacovigilance information available and will require justification by the party making the referral.

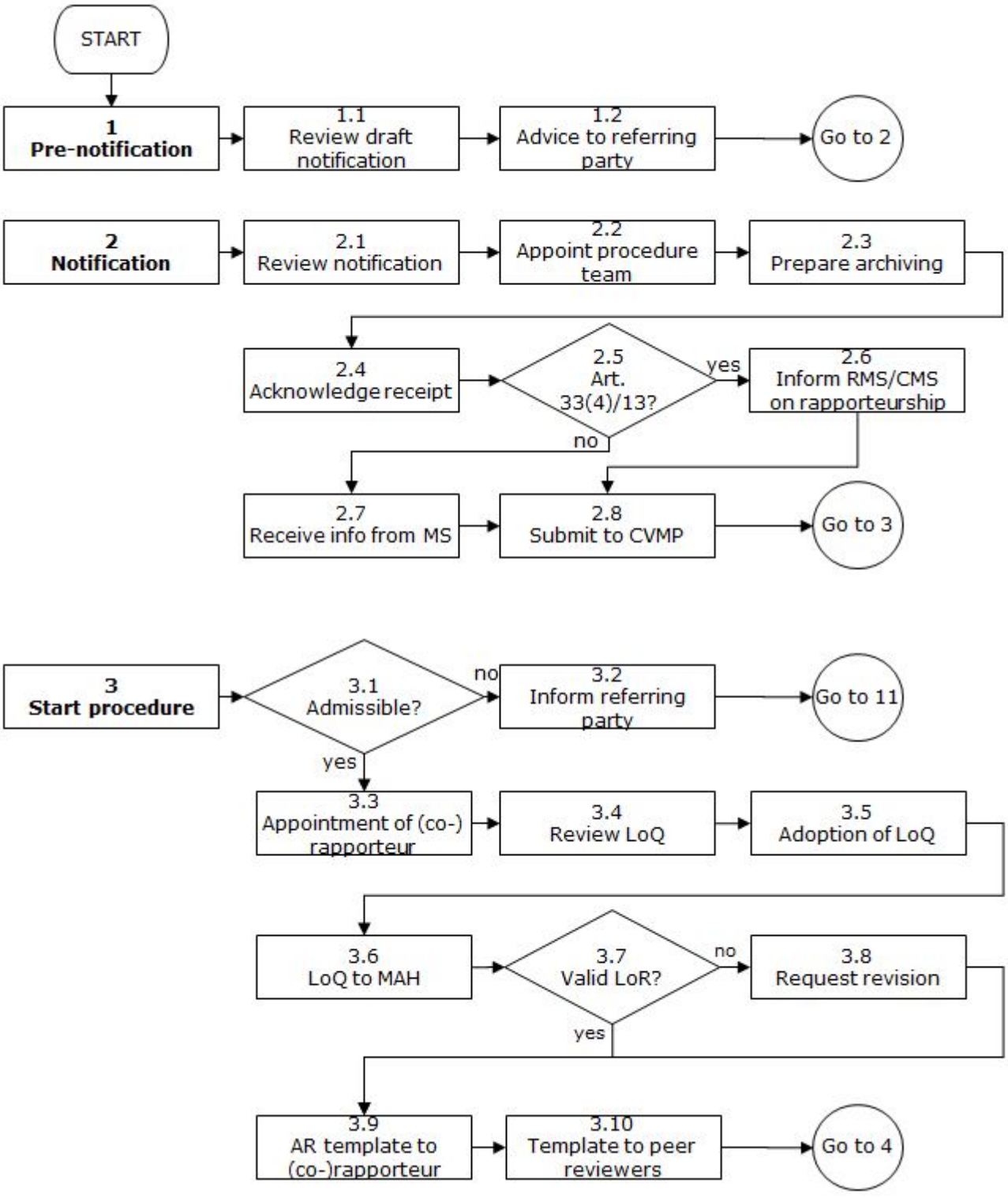
- Appointment and responsibilities of rapporteur and co-rapporteur for procedures regarding veterinary medicinal products (EMA/CVMP/468877/2009);
- The linguistic review process of product information in the centralised procedure – veterinary;
- SOP/PDM/1004 on core master files of medicinal products for human and veterinary use following the centralised and referrals procedures.

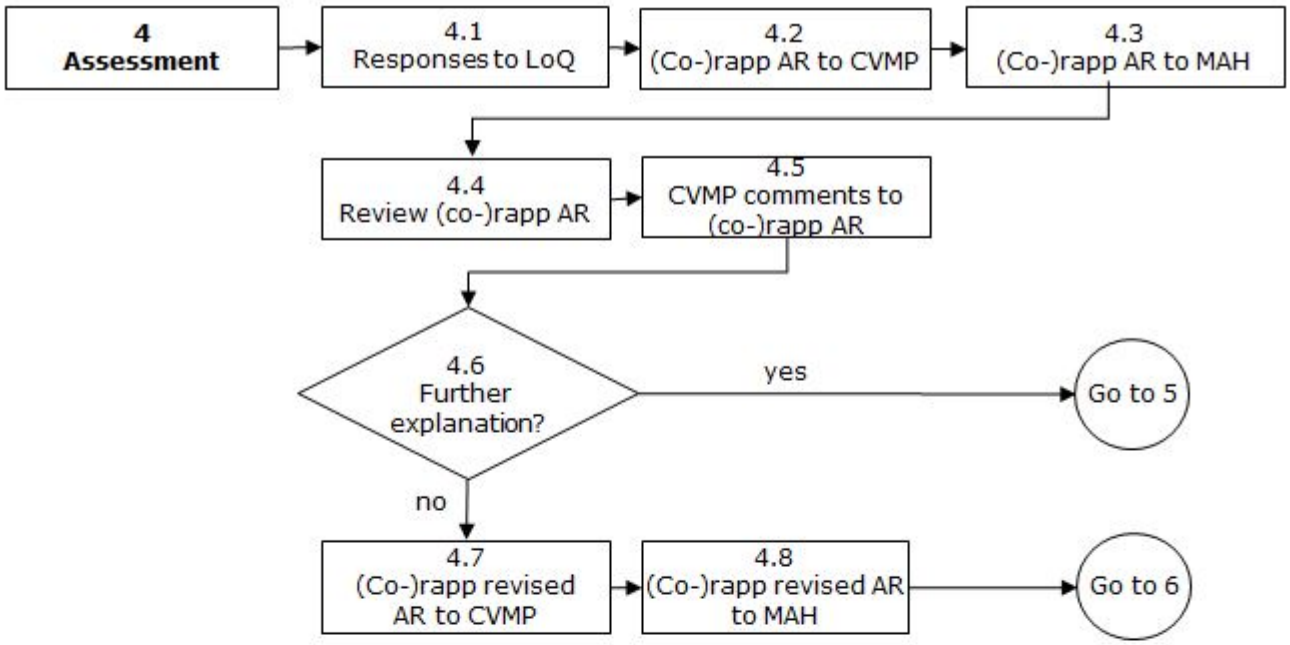
7. Definitions

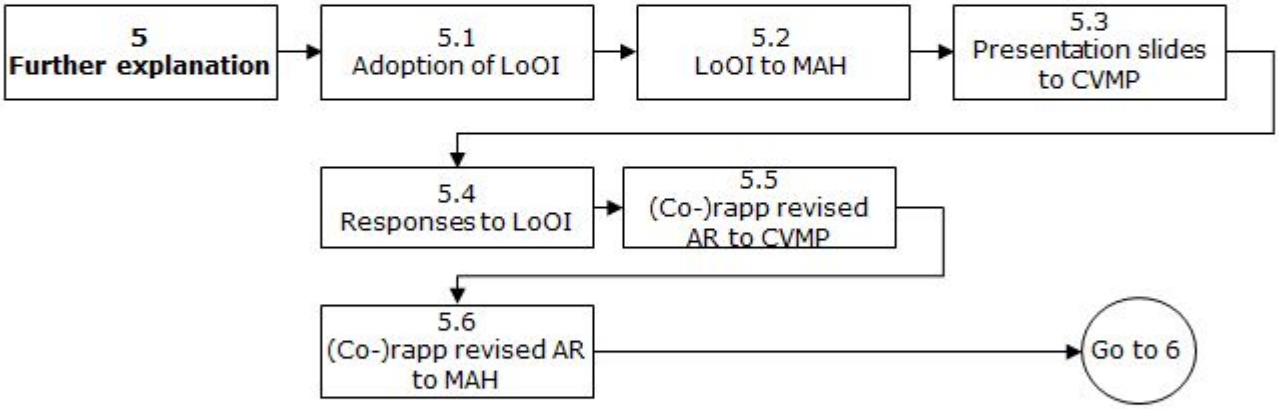
AA	Administrative assistant
APH	Animal and Public Health
AR	Assessment report
AST	Assistant allocated to support the procedure
Checklist	Agency-internal document describing all steps involved in a specific procedure. In this case refers to checklist on post opinion phase following CVMP opinions on procedures under Articles 33(4), 34, 35 and 78 of Directive 2001/82/EC, as well as Article 13 of Commission Regulation (EC) No 1234/2008
CMDv	Coordination group for Mutual recogntion and Decentralised procedures (veterinary)
c-MF	Core Master File
CMS	Concerned Member State
Co-rapporteur	CVMP member and/or alternate appointed for the assessment of the matter
CV	*Curriculum Vitae*
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised procedure
DEM	Development and Evaluation of Veterinary Medicines
DREAM	Document Records Electronic Archive Management system
EC	European Commission
EMA	European Medicines Agency
HDep	Head of Department (here: Head of Veterinary Medicines Department)
HSer	Head of Service (Head of Veterinary Regulatory and Organisational Support, Head of Animal and Public Health and Head of Development and Evaluation of Veterinary Medicines)
LoOI	List of outstanding issues
LoQ	List of questions
MAH	Marketing authorisation holder
MRP	Mutual recognition procedure
MS	Member State(s)
Peer reviewer	CVMP member and/or alternate (who is not acting as rapporteur or co-rapporteur in the procedure) tasked with quality assurance of CVMP documents (in this case related to referral procedures)
PIQ	Product information quality
PM	Scientific administrator appointed as project manager to coordinate the referral
Procedure shared mailbox	Agency mailbox to collect procedure-specific electronic correspondence; the email addresses are based on the procedure name and number
QRD	Quality review of documents

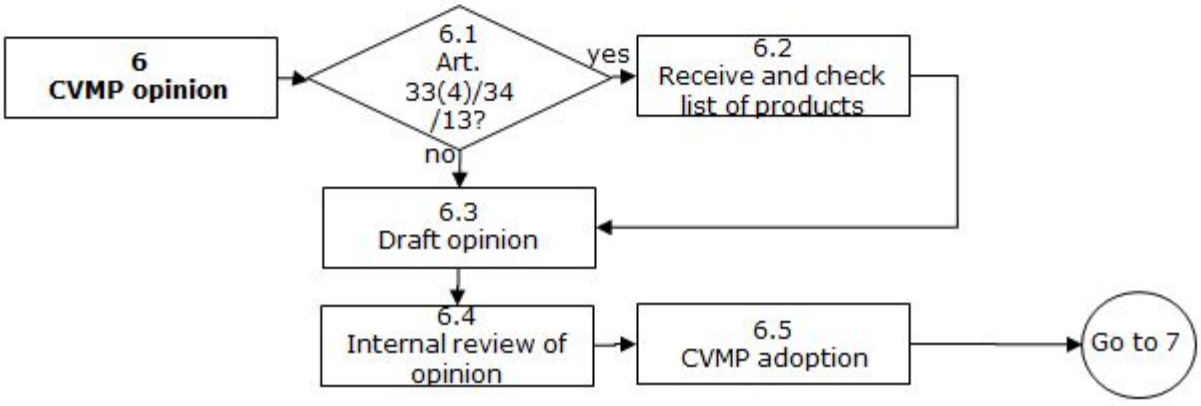
Rapporteur	CVMP member and/or alternate appointed for the assessment of the matter
RMS	Reference Member State
SOP	Standard operating procedure
VMP	Veterinary medicinal product
VROS	Veterinary Regulatory and Organisational Support

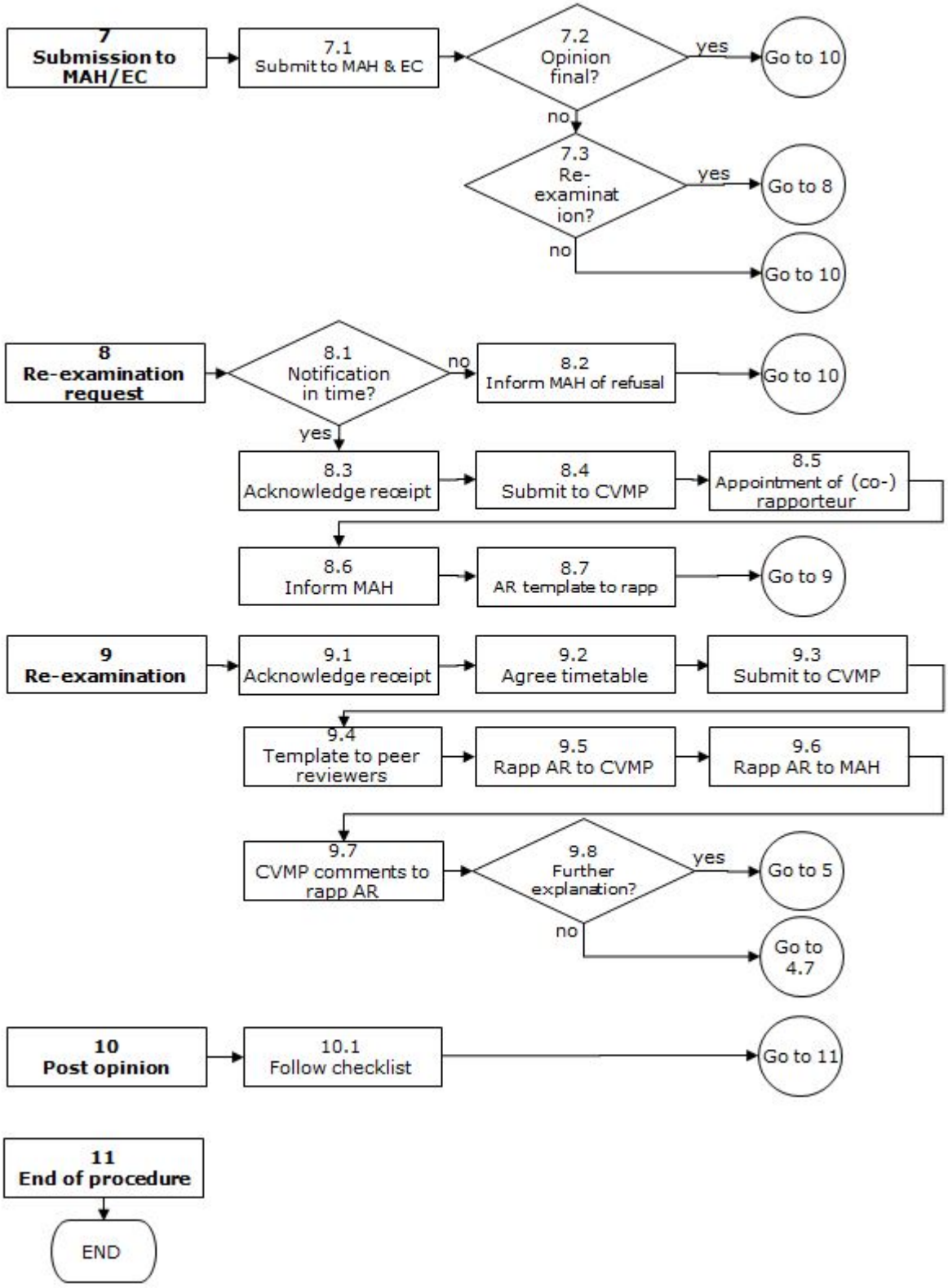
8. Process map(s)/ flow chart(s)




4
Assessment
4.1
Responses to LoQ
4.2
(Co-)rapp AR to CVMP
4.3
(Co-)rapp AR to MAH
4.4
Review (co-)rapp AR
4.5
CVMP comments to (co-)rapp AR
4.6
Further explanation?
yes
Go to 5
no
4.7
(Co-)rapp revised AR to CVMP
4.8
(Co-)rapp revised AR to MAH
Go to 6


5
Further explanation
5.1
Adoption of LoOI
5.2
LoOI to MAH
5.3
Presentation slides to CVMP
5.4
Responses to LoOI
5.5
(Co-)rapp revised AR to CVMP
5.6
(Co-)rapp revised AR to MAH
Go to 6


6
CVMP opinion
6.1
Art. 33(4)/34 /13?
yes
6.2
Receive and check list of products
no
6.3
Draft opinion
6.4
Internal review of opinion
6.5
CVMP adoption
Go to 7


7
Submission to MAH/EC
7.1
Submit to MAH & EC
7.2
Opinion final?
yes
Go to 10
no
7.3
Re-examination?
yes
Go to 8
no
Go to 10
8
Re-examination request
8.1
Notification in time?
no
8.2
Inform MAH of refusal
Go to 10
yes
8.3
Acknowledge receipt
8.4
Submit to CVMP
8.5
Appointment of (co-) rapporteur
8.6
Inform MAH
8.7
AR template to rapp
Go to 9
9
Re-examination
9.1
Acknowledge receipt
9.2
Agree timetable
9.3
Submit to CVMP
9.4
Template to peer reviewers
9.5
Rapp AR to CVMP
9.6
Rapp AR to MAH
9.7
CVMP comments to rapp AR
9.8
Further explanation?
yes
Go to 5
no
Go to 4.7
10
Post opinion
10.1
Follow checklist
Go to 11
11
End of procedure
END

9. Procedure

Step	Action	Responsibility
1.0	**Pre-notification**	
1.1	Upon receipt of the draft notification, discuss the matter to be referred, the legal basis and adequacy of notification with project managers in VROS, CMDv secretariat, HDep and the Legal Department, as appropriate.	HSer VROS
1.2	Advise the referring party (MS(s), EC or applicant/MAH) of comments on the notification including legal basis, in accordance with internal EMA discussions. Proceed to 2.0	HSer VROS
2.0	**Receipt of formal notification and initiation of procedure**	
2.1	Upon receipt of the official notification, discuss the matter, the legal basis and the adequacy of the notification with the project managers in VROS, CMDv secretariat, HDep and the Legal Department, as appropriate, unless already done at step 1.1.	HSer VROS
2.2	Allocate the procedure to a project manager and assistant and create team in liaison with HSer APH and/or DEM (including DEM and APH members, as appropriate).	HSer VROS
2.3	Allocate procedure number and create an electronic folder in DREAM (including subfolders), as well as c-MF. Send request to IT for a procedure shared mailbox to be created and inform the PM when this has been set up.	AA
2.4	Acknowledge receipt of the notification using model "*01a Confirmation of receipt of notification (email)*".	PM
2.5	Is the referral notified under Article 33(4) of Directive 2001/82/EC or Article 13 of Commission Regulation (EC) No 1234/2008? If yes, proceed to 2.6 If no, proceed to 2.7	
2.6	Send email to CVMP members from RMS and objecting CMS regarding (co)-rapporteurship and attach template for list of questions and draft timetable using models "*01d (Co-)rapporteurship for Art 33(4) or 13 referrals (email)*", "*02b CVMP Referral list of questions*" and "*02c Timetable for referral procedure*". Proceed to 2.8	PM
2.7	Inform all MSs of the receipt of the notification and request information on the national marketing authorisations and contact details for the applicants/MAHs of the products concerned by the procedure, using models "*01b Letter to MS*" and "*01c Product list to be completed by the MSs (form)*". Ensure timely receipt of information and send reminder(s), if necessary.	PM/AST
2.8	Include the following documents in the agenda of the next CVMP meeting • Referral notification for confirmation of admissibility of referral; • Discussion document with a clear summary of the matter, discussion of assessment approach and procedural details (timetable, approach for appointment of (co-)rapporteurs and peer reviewers) for CVMP decision, where appropriate; *NB: For the preparation of the discussion document the PM should consult with CMDv secretariat, APH and/or DEM team member, as*	PM/AST

Step	Action	Responsibility
	appropriate; • List of products concerned, where appropriate. Proceed to 3.0	
3.0	**Start of procedure**	
3.1	*CVMP meeting (Day 1)* Ensure the CVMP considers the referral notification. Is the referral admissible (outcome of step 2.1 to be considered)? If yes, go to 3.3 If no, go to 3.2	PM
3.2	Inform sender of notification, providing reasons for refusal of the referral using model "*02f Letter to notifying MS or MAH - Referral refused*". Proceed directly to 11.0	PM/AST
3.3	Ensure the CVMP: • Starts the referral procedure; • Considers the assessment approach and appoints rapporteur, co-rapporteur and peer reviewers.	PM
3.4	Review the draft list of questions in liaison with APH and/or DEM team member, as appropriate and discuss with the rapporteur/co-rapporteur, if necessary.	PM
3.5	Ensure the CVMP: • Considers the necessary evaluation period (60 days[2] or up to 150 days[3]) and adopts timetable for the procedure using model "*02c Timetable for referral procedure*"; • Adopts list of questions using model "*02b CVMP Referral list of questions*".	PM
3.6	*Clock stop*[4] Send letter to the applicant(s)/MAH(s) using model "*02a Letter to MAH - Start of procedure and LoQ*" and enclose the referral notification, CVMP list of questions, timetable, model for letter of representation and list of products concerned, if appropriate.	PM/AST
3.7	Confirm receipt and adequacy of the letters of representation received. Are the letters of representation admissible? If yes, go to 3.9 If no, go to 3.8	PM/AST
3.8	Request revised letters of representation using model texts from "*02e Email text examples for LoRs for referrals*".	AST
3.9	Prepare template of draft assessment report using model "*Rapporteur's AR*" in liaison with APH and/or DEM team member, as appropriate, adjusting template to specific needs of the referral under consideration and send to rapporteur and, if separate reports, to co-rapporteur.	PM
3.10	Prepare template of peer review report using model "*04e Peer review template*" and send to peer reviewers including information on due date, using model "*04f Email to peer reviewers - Peer review template*". Proceed to 4.0	PM

[2] For procedures under Article under Article 33(4) of Directive 2001/82/EC or Article 13 of Commission Regulation (EC) No 1234/2008
[3] For procedures under Article 34 and Article 35 of Directive 2001/82/EC
[4] In general, the time given to the applicant(s)/MAH(s) to answer the CVMP list of questions should not exceed 3 months.

Step	Action	Responsibility
4.0	**Scientific assessment**	
4.1	*Clock re-start (Day 2)* Ensure that responses to the list of questions have been received by EMA, rapporteur, co-rapporteur and the CVMP.	PM
4.2	*(Co-)rapporteur's assessment(s) (Day 20[5])* Ensure that (co-)rapporteur's assessment report(s) (rapporteur's assessment report with co-rapporteur's critique or individual reports from rapporteur and co-rapporteur) is/are circulated to CVMP members and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org), and send reminder to (co-)rapporteur, if necessary.	PM/AST
4.3	Send (co-)rapporteur's assessment report(s) (with co-rapporteur's critique) to applicant(s)/MAH(s) including information on the possibility to request to provide an oral explanation to the CVMP using model "*04a Letter to MAH - Rapporteur's assessment report*". The attachments should be in a .zip file, so the relevant versions of the documents can be added to the cMF.	PM/AST
4.4	Consider the (co-)rapporteur's assessment report(s) in liaison with APH and/or DEM team member, as appropriate, and send comments to the rapporteur/co-rapporteur, if necessary.	PM
4.5	*Comments of peer reviewers and remaining CVMP members on rapporteur's assessment report (Day 25)* Ensure that comments on (co-)rapporteur's assessment report(s) are circulated to CVMP and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org).	PM/AST
4.6	*CVMP discussion (Day 30)* Ensure the CVMP discusses the (co-)rapporteur's assessment report(s) including any comments received and considers the need for further information from the applicant(s)/MAH(s) to be provided in writing and/or in oral explanation. Is further information required or has an oral explanation been requested by applicant(s)/MAH(s)? If yes, go to 5.0 If no, go to 4.7	PM
4.7	*(Co-)rapporteur's revised assessment (day 45)* Ensure that (co-)rapporteur's revised assessment report is circulated to CVMP members and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org), and send reminder to (co-)rapporteur, if necessary.	PM/AST
4.8	Send revised (co-)rapporteur's assessment report(s) (with co-rapporteur's critique) to applicant(s)/MAH(s) including information on the possibility to request to provide an oral explanation to the CVMP using model "*04a Letter to MAH - Rapporteur's assessment report*", if necessary. The attachments should be in a .zip file, so the relevant versions of the documents can be added to the cMF. Proceed to 6.0	PM/AST
5.0	**Outstanding issues to be addressed in writing and/or oral explanation**	
5.1	*Adoption of list of outstanding issues (Day 30)* Consider the proposed list of outstanding issues in liaison with APH and/or DEM team member, as appropriate and discuss with the	PM

[5] For procedures under Article 34 and Article 35 of Directive 2001/82/EC in case an evaluation period of more than 60 days is agreed, the dates indicated here would have to be adjusted depending on the evaluation period. Furthermore, other dates apply during re-examination procedures.

Step	Action	Responsibility
	rapporteur/co-rapporteur, if necessary. Ensure the CVMP adopts a revised timetable and list of outstanding issues to be addressed in writing and/or at oral explanation.	
5.2	*Clock stop*[6] Send list of outstanding issues to applicant(s)/MAH(s) with an invitation for an oral explanation, if applicable, using model "*04b Letter to MAH – List of outstanding issues*" or "*04c Letter to MAH – LoOI and invitation for OE*". *NB: In case an oral explanation is scheduled, request presentation and CVs of applicant/MAH representatives in time for 1st mailing of the CVMP meeting when the explanation will be held.* Ensure timely receipt of presentation(s) and CVs from applicant(s)/MAH(s) and send reminder(s), if necessary.	PM/AST
5.3	In case of oral explanation circulate the revised timetable, list of outstanding issues, latest version of rapporteur's assessment report, presentation(s) of the applicant(s)/MAH(s) and CVs of applicant(s)/MAH(s) representatives to CVMP with the 1st mailing of the CVMP meeting at which the explanation will be given.	PM/AST
5.4	*Clock re-start (Day 31)* Ensure that responses to the list of outstanding issues (in writing and/or at oral explanation) have been received by EMA, rapporteur, co-rapporteur and the CVMP.	PM
5.5	*Revised Assessment (Day 45)* Ensure that (co-)rapporteur's revised assessment report is circulated to CVMP members and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org), and send reminder to (co-)rapporteur, if necessary.	PM/AST
5.6	Send revised (co-)rapporteur's assessment report(s) to applicant(s)/MAH(s) using model "*04a Letter to MAH - Rapporteur's assessment report*". The attachments should be in a .zip file, so the relevant versions of the documents can be added to the cMF. Proceed to 6.0	PM/AST
6.0	**CVMP opinion**	
6.1	Is the referral a procedure under Article 33(4) or Article 34 of Directive 2001/82/EC, or Article 13 of Commission Regulation (EC) No 1234/2008? If yes, go to 6.2 If no, go to 6.3	
6.2	Request the applicant/MAH to fill in the table with list of products (Annex I of the CVMP opinion). Once received, check for any inconsistencies and if necessary send it to MSs for confirmation.	PM/AST
6.3	Prepare draft CVMP opinion using models "*05a-d CVMP opinion*" and change the (co-)rapporteur's revised assessment report to draft CVMP referral assessment report, in liaison with APH and/or DEM team member, as appropriate; and circulate to CVMP for adoption at the next meeting.	PM
6.4	Send the draft CVMP opinion and assessment report for internal review to HSer VROS, APH, DEM as appropriate, and HDep.	PM
6.5	*CVMP adoption of opinion and assessment report (Day 60)* Finalise opinion and CVMP assessment report following CVMP discussion/adoption, in liaison with APH and/or DEM team member, as appropriate.	PM

[6] In general, the time given to the applicant(s)/MAH(s) to answer the CVMP list of outstanding issues should not exceed 2 months.

Step	Action	Responsibility
	Proceed to 7.0	
7.0	**Submission of CVMP opinion to applicant(s)/MAH(s) and submission to European Commission**	
7.1	Prepare submission of CVMP opinion to the applicant(s)/MAH(s) and to the European Commission for adoption by Standing Committee, following '*Checklist on post opinion phase following CVMP opinions on procedures under Articles 33(4), 34, 35 and 78 of Directive 2001/82/EC, as well as Article 13 of Commission Regulation (EC) No 1234/2008*'.	AST
7.2	Is this the final opinion after re-examination? If yes, go to 10.0 If no, go to 7.3	PM
7.3	Does/do the applicant(s)/MAH(s) request re-examination of the CVMP opinion? If yes, go to 8.0 If no, go to 10.0	PM
8.0	**Re-examination request**	
8.1	Receipt of written notice of the intention to request re-examination of the CVMP opinion within 15 days[7] of receipt[8] of the opinion by the applicant(s)/MAH(s). Was the re-examination request received in time? If yes, go to 8.3 If no, go to 8.2	PM
8.2	Notify applicant(s)/MAH(s) that submission deadline for notification of intention to request re-examination of the opinion has passed. Proceed to 10.0	PM
8.3	Acknowledge receipt of the notification of intention to request re-examination.	PM
8.4	Include notification on the agenda of the next CVMP meeting. Prepare a background note with a clear summary of the matter indicating the deadline for receipt of the grounds for re-examination and the likely time schedule for the evaluation.	PM
8.5	Ensure the CVMP appoints rapporteur, co-rapporteur and peer reviewers to assess the grounds for re-examination.	PM
8.6	Inform applicant(s)/MAH(s) of the appointment of the rapporteur and co-rapporteur including information on the possibility to request to provide an oral explanations to the CVMP using model "*06a Re-examination rapporteurs to MAH (letter)*".	PM/AST
8.7	Prepare draft rapporetur's assessment report for the re-examination of the CVMP opinion in liaison with APH and/or DEM team member, as appropriate, and send to rapporteur. Proceed to 9.0	PM
9.0	**Assessment of the grounds for re-examination**	
9.1	Upon receipt of the grounds for re-examination acknowledge receipt of the documentation.	PM
9.2	Prepare a draft timetable for the re-examination procedure and agree	PM

[7] Days are counted as calendar days. The period starts at the day following the receipt of the referral opinion. Where the last day in a specific period falls on a Saturday, Sunday or Public Holiday the following working day will be considered as the final day.

[8] The day of receipt of the opinion is the day when the applicant/MAH received the opinion by Eudralink. In the covering letter the EMA Secretariat advises the applicant(s)/MAH(s) on the deadline of 15 days to notify the intention to request the re-examination of the CVMP opinion.

Step	Action	Responsibility
	it with the rapporteur and co-rapporteur. Ensure rapporteur and co-rapporteur have received the grounds for re-examination.	
9.3	Include the topic on the agenda for the next CVMP meeting, and include the grounds for re-examination as well as the timetable.	PM
9.4	Prepare template for peer review report using model "*04e Peer review template*" and send to peer reviewers including information on due date, using model "*04f Email to peer reviewers - Peer review template*".	PM
9.5	Ensure that rapporteur's assessment of the grounds for re-examination and co-rapporteur's critique are circulated to CVMP members and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org), and send reminder(s) to (co-)rapporteur, if necessary.	PM/AST
9.6	Send rapporteur's assessment report with the co-rapporteur's critique to applicant(s)/MAH(s).	PM/AST
9.7	Ensure that comments on rapporteur's assessment report and co-rapporteur's critique are circulated to CVMP and EMA via Eudranet to *All Veterinary CVMP* (list-v-cvmp@eudra.org).	PM/AST
9.8	Ensure the CVMP discusses the rapporteur's assessment report with the co-rapporteur's critique including any comments received and considers the need for further information from the applicant(s)/MAH(s) to be provided in writing and/or in oral explanation[9]. Is further information required or has an oral explanation been requested by applicant(s)/MAH(s)? If yes, go to 5.0 If no, go to 4.7	PM
10.0	**Post opinion**	
10.1	Follow the '*Checklist on post opinion phase following CVMP opinions on procedures under Articles 33(4), 34, 35 and 78 of Directive 2001/82/EC, as well as Article 13 of Commission Regulation (EC) No 1234/2008',* and after a Commission Implementing Decision and publication of the relevant information on the EMA website check the completeness of the electronic c-MF. Declare the relevant correspondence and documents as a record in DREAM for the electronic c-MF, if not done previously. Proceed to 11.0.	AST
11.0	**End of procedure**	

10. Records

Electronic copies of corespondence and documents related to the procedure are saved in the appropriately labelled folder in DREAM and core master file.

[9] No clock stop is allowed during the re-examination phase.