EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Evaluation procedure for applications and requests for the establishment or review of Maximum Residue Limits (MRLs)		
Status: **PUBLIC**		Document no.: SOP/V/4150
Lead author	Approver	Effective date: 05-MAY-17
Name: Sylvia Jahromy	Name: Isaura Duarte	Review date: 05-MAY-20
Signature: on file	Signature: on file	Supersedes: SOP/V/4051 (15-AUG-15) SOP/V/4052 (01-DEC-15) SOP/V/4053 (01-DEC-15)
Date: 27-APR-17	Date: 27-APR-17	TrackWise record no.: 5228

1. Purpose

This SOP serves to describe the procedure for the establishment or review of maximum residue limits (MRLs) incl. re-examination, where applicable. It does not describe the processing of requests for inclusion of a substance in the so-called “out of scope” list.

2. Scope

This SOP applies to the appointed procedure teams for the establishment or review of MRLs, within the Veterinary Medicines Division.

This SOP relates to standard and accelerated procedures for the establishment or review of MRLs under the following articles of Regulation (EC) No 470/2009:

- applications under Article 3;
- requests under Article 9;
- applications for new substances included in biocidal products under Article 10;
- review requests under Article 11;
- accelerated procedures under Article 15; and
- requests for extrapolation under Article 27.

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

The timelines of the accelerated procedures are stated in brackets after the timelines for the standard procedures, e. g. 120 (90) days.

This SOP includes also the procedure for the re-examination of CVMP opinions on applications submitted to the Agency under Articles 3, 10 and 15 of Regulation (EC) No 470/2009.

3. Responsibilities

It is the responsibility of the Head of the Veterinary Medicines Department (delegated to the relevant Head of Service) to ensure that this procedure is adhered to within their own Department/Service. 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

New SOP.

New SOP/WIN structure implemented in the Division; this SOP implements the revised procedures for MRLs and includes the previously separate SOPs on Article 11 and Article 27 procedures into one main SOP for all MRL procedures.

5. Documents needed for this SOP

- Procedure templates in SIAMED (without pre-submission)
- Pre-submission templates in X:\Templates\Others\Vet\MRLs
- Procedure checklist in DREAM (EMA/153767/2017)

6. Related documents

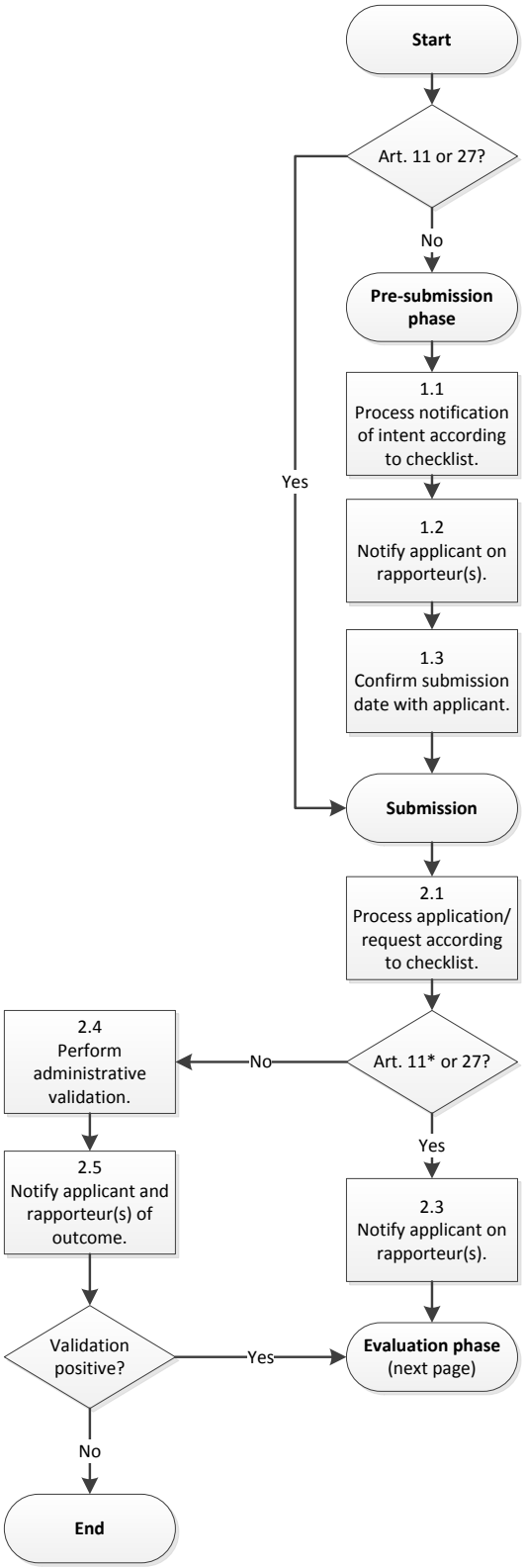
- Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009, laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council
- Volume 8 – Notice to Applicants and Note for Guidance: Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin
- Pre-submission guidance for MRL applications (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000283.jsp&mid=WC0b01ac058002da5e)
- List of recommended submission dates (published annually on the Agency website under http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000165.jsp&mid=WC0b01ac058002d89b)
- SOP/PDM/1004 on Core Master Files of medicinal products for human and veterinary use following the centralised procedure

7. Definitions

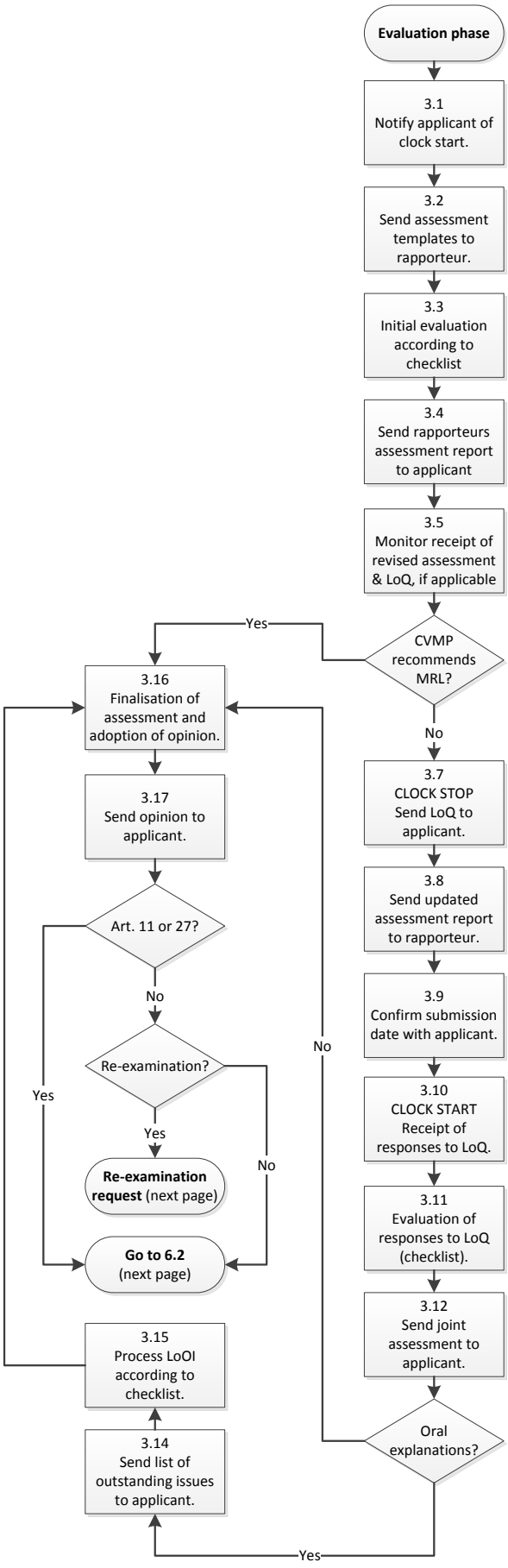
AA	Administrative Assistant (here: assigned to vet.applications team)
APH	Animal and Public Health service (in the Veterinary Medicines department)
Applicant	A person submitting an application for the establishment of maximum residue limits under Article 3, 10 or 15 of Regulation (EC) No. 470/2009. For the purpose of this SOP the term “applicant” also refers to Member States or the European Commission when submitting a request to the Agency for the establishment or review of MRLs under Article 9, 11 or 27 of Regulation (EC) No. 470/2009.
EU-RL	European Union Reference Laboratory
Checklist	Agency-internal document describing all administrative steps involved in a specific procedure. In this case refers to checklist on MRL procedures, unless otherwise specified.
cMF	Core Master File
CV	Curriculum Vitae
CVMP	Committee for Medicinal Products for Veterinary Use
EPMAR	European Public MRL Assessment Report
DREAM	Document Records Electronic Archive Management
EFTA	European Free Trade Association
HDep	Head of Department (here: Head of Veterinary Medicines department)
HSer	Head of Service (here: Head of VROS or Head of APH)
LoOI	List of outstanding issues
LoQ	List of questions
MRL	Maximum residue limit
MRL application	Application for the establishment of maximum residue limits
PC	Procedure Coordinator, typically an Assistant, assigned to the management of the procedure
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 the establishment of maximum residue limits)
(Co-)Rapporteur	CVMP member and/or alternate appointed for the assessment of the application
SIAMED	Product information and application tracking system of the Agency
S/CL	Scientific administrator assigned as the scientific/content lead for the procedure
SOP	Standard operating procedure; Agency document describing steps involved in a specific procedure
VMP	Veterinary medicinal product

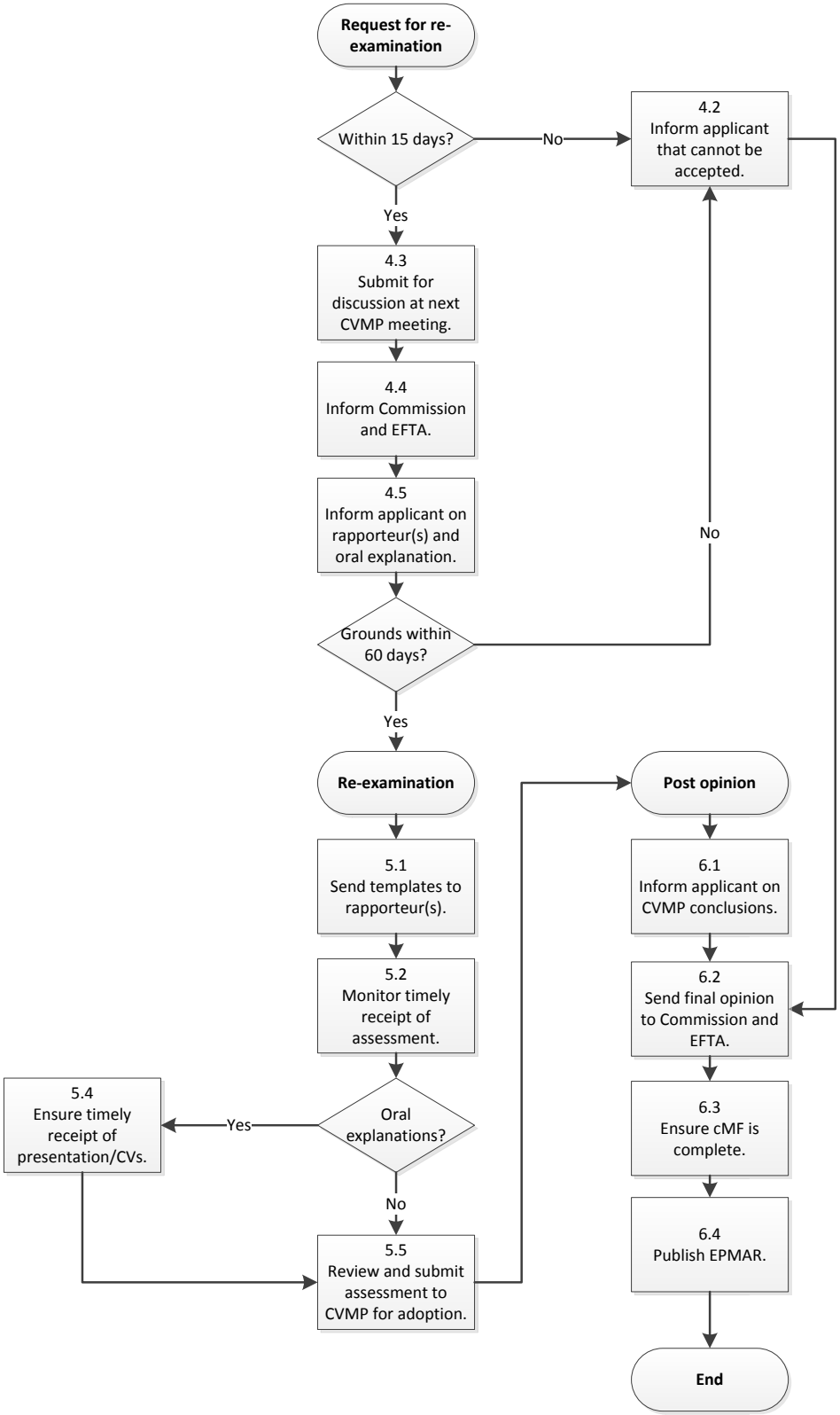
VO	Validating Officer, responsible for the validation of the application dossier (here: Administrative Assistant in VROS)
VROS	Veterinary Regulatory and Organisational Support service (in the Veterinary Medicines department)
WIN	Work Instructions

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



* Except where the review is requested by the original applicant


Evaluation phase
3.1
Notify applicant of clock start.
3.2
Send assessment templates to rapporteur.
3.3
Initial evaluation according to checklist
3.4
Send rapporteurs assessment report to applicant
3.5
Monitor receipt of revised assessment & LoQ, if applicable
CVMP recommends MRL?
Yes
No
3.16
Finalisation of assessment and adoption of opinion.
3.17
Send opinion to applicant.
Art. 11 or 27?
No
Re-examination?
Yes
No
Yes
Re-examination request (next page)
Go to 6.2 (next page)
3.7
CLOCK STOP
Send LoQ to applicant.
3.8
Send updated assessment report to rapporteur.
3.9
Confirm submission date with applicant.
3.10
CLOCK START
Receipt of responses to LoQ.
3.11
Evaluation of responses to LoQ (checklist).
3.12
Send joint assessment to applicant.
Oral explanations?
No
Yes
3.14
Send list of outstanding issues to applicant.
3.15
Process LoOI according to checklist.


Request for re-examination
Within 15 days?
No
4.2
Inform applicant that cannot be accepted.
Yes
4.3
Submit for discussion at next CVMP meeting.
4.4
Inform Commission and EFTA.
4.5
Inform applicant on rapporteur(s) and oral explanation.
No
Grounds within 60 days?
Yes
Re-examination
5.1
Send templates to rapporteur(s).
5.2
Monitor timely receipt of assessment.
5.4
Ensure timely receipt of presentation/CVs.
Yes
Oral explanations?
No
5.5
Review and submit assessment to CVMP for adoption.
Post opinion
6.1
Inform applicant on CVMP conclusions.
6.2
Send final opinion to Commission and EFTA.
6.3
Ensure cMF is complete.
6.4
Publish EPMAR.
End

9. Procedure

Step	Action	Responsibility
0.0	Is the procedure a request under Art. 11 or Art. 27 of Regulation (EC) 470/2009? If **yes**, go to 2.0 If **no**, go to 1.0.	
1.0	**Pre-submission phase**	
1.1	*Notification of intention to submit an MRL application is usually received **3 months** before the intended submission*[1]. Upon receipt of letter of intent the notification is processed following the procedural steps described in the checklist.	PC
1.2	*Appointment of rapporteur and co-rapporteur, if applicable, as well as peer reviewers by CVMP:* Notify the applicant of the appointed rapporteur and co-rapporteur, if applicable, and of the recommended submission date(s).	PC
1.3	*Approx. 1 month before intended submission:* Confirm submission date with applicant; amend recommended submission dates & inform rapporteur(s), if applicable.	PC
2.0	**Submission and validation of the MRL application**	
2.1	Upon receipt the MRL application or request is processed following the procedural steps described in the checklist.	AA
2.2	Is the procedure a request under Art. 11 or Art. 27 of Regulation (EC) 470/2009? If **yes**, go to 2.3[2] If **no**, go to 2.4	
2.3	*Appointment of rapporteur, co-rapporteur, and peer reviewers, as applicable, by CVMP:* Notify the applicant of the appointed rapporteur and co-rapporteur, as applicable. Proceed to 3.0	PC
2.4	*Within 13 working days*: Carry out administrative validation.	VO
2.5	Notify applicant, rapporteur and co-rapporteur of the outcome of the validation of the application.	VO
2.6	Was the validation positive? If **yes**, go to 3.0 If **no**, proceed to 7.0 (end of procedure)	
3.0	**210 (120)[3] day Evaluation Phase**	
3.1	Notify applicant of clock start: day 1. If applicable, notify relevant EU-RL of the start of the evaluation procedure.	PC
3.2	Send the assessment report and scientific overview including list of questions templates to the rapporteur.	PC

[1] An MRL application shall be submitted **at least 6 months** before the application for the concerned marketing authorisation for the VMP.
[2] Except where the review is requested by the original applicant
[3] The number of days in brackets refers to the timeline for an accelerated procedure in accordance with Art. 15 of Regulation (EC) 470/2009

Step	Action	Responsibility
3.3	Initial evaluation within 120 (90) days following procedural steps described in checklist. Monitor timely receipt of: • draft assessment report and scientific overview including list of questions, if applicable, from rapporteur • critique of rapporteur's assessment report from the co-rapporteur, if applicable • comments on assessment report from the peer reviewers, CVMP members and EU-RL, as applicable.	PC
3.4	Send rapporteur's assessment report (incl. co-rapporteur's critique, if applicable) to applicant.	PC
3.5	Monitor receipt of revised scientific overview including list of questions, if applicable, from the rapporteur.	PC
3.6	*Conclusion on initial evaluation and adoption of the scientific overview, if applicable, by CVMP (Day 120 (90)).* Can the CVMP make a recommendation for the establishment of MRLs? If **yes**, go to 3.16 If **no**, go to 3.7	
3.7	***Clock Stop*** Send scientific overview with LoQ to applicant[4]. If applicable, inform EU-RL on CVMP conclusions with regard to the analytical method.	PC
3.8	Update rapporteur's assessment report in order to include the relevant comments from co-rapporteur, peer reviewers and other CVMP members in line with conclusions at day 120 (90). Send updated assessment report to rapporteur and co-rapporteur, if applicable, for agreement.	S/CL PC
3.9	Confirm the exact submission date for responses to the LoQ with the applicant 2 months prior to the deadline.	PC
3.10	Once the response[5] has been received on the agreed date according to submission dates, ***restart clock*** of the remaining evaluation period for days 121-210 (91-120) as described in checklist. If the scientific overview included questions on the analytical method inform EU-RL on the submission of the response to the LoQ and forward them to the EU-RL.	PC
3.11	*Evaluation of responses to list of questions within the remaining 90 (30) days following procedural steps described in checklist*. Monitor timely receipt of: • updated joint assessment report with assessment of responses to LoQ from rapporteur • comments on assessment report from the peer reviewers, CVMP members and EU-RL, as applicable.	PC
3.12	Send joint assessment report to applicant.	PC

[4] The Agency identifies an approximate submission date in the cover letter to the status report and LoQ; in general 6 months are granted to respond to the LoQ. This timeframe may be extended only exceptionally upon request and if duly justified.

[5] One consolidated response to all questions should be submitted

Step	Action	Responsibility
3.13	Has CVMP agreed to request or grant an oral explanation (and when to hear it) (Day 180/accelerated Day 120)? If **yes**, go to 3.14 If **no**, go to 3.16	
3.14	***Clock stop*** Send list of outstanding issues to applicant, if applicable. Process according to steps described in checklist.	PC
3.15	Monitor timely receipt of revised rapporteurs' assessment report following oral explanation from the rapporteur. Finalise assessment report and opinion including EPMAR for adoption by CVMP according to steps described in checklist, including relevant steps relating to legal scrutiny of the documents.	PC S/CL
3.16	Monitor finalisation of assessment report and adoption of opinion including EPMAR for recommendation of MRL(s) at day 210(120). *NB: If there is no LoQ at day 120(90), the opinion will be adopted at day 150(120).*	PC
3.17	Send opinion including EPMAR and CVMP assessment report to applicant, European Commission and EFTA according to procedural steps described in the checklist.	PC
3.18	Is the procedure a request under Art. 11 or Art. 27 of Regulation (EC) 470/2009? If **yes**, go to 6.2 If **no**, go to 3.19	
3.19	Did the applicant request a re-examination[6]? If **yes**, go to 4.0 If **no**, go to 6.2	
4.0	**Receipt of a notification to request re-examination of CVMP opinion by the applicant**	
4.1	Was the notification received within the 15 day deadline? If **yes**, go to 4.3 If **no**, go to 4.2	
4.2	Inform applicant that re-examination request cannot be accepted as deadline has passed. Go to 6.2	PC
4.3	Inform applicant of submission of notification to CVMP, including notification of deadline for submission of detailed grounds for re-examination (see *Annex IV*). Submit notification for discussion (and decision on oral explanation, if requested by applicant) and appointment of rapporteur (and co-rapporteur, if appropriate) at next CVMP meeting.	PC PC
4.4	Inform European Commission (and EFTA authorities) of receipt of notification to request re-examination.	PC
4.5	*Within 5 days after CVMP meeting:* Inform applicant on rapporteur(s) for the re-examination and of decision on oral explanations, if applicable.	PC
4.6	Were the detailed grounds received within the 60 day deadline? If **yes**, go to 5.0 If **no**, go to 4.2	

[6] Within 15 days of receipt of the opinion, the applicant may provide written notice to the Agency secretariat of his intention to request re-examination of the recommendation (see *Annex IV*)

Step	Action	Responsibility
5.0	**Re-examination of CVMP opinion**	
5.1	Send the template for the assessment of the grounds for re-examination and EPMAR (previously adopted) in electronic format to the rapporteur for the assessment of the re-examination, to facilitate the inclusion of changes to the EPMAR. Submit detailed grounds for discussion at next CVMP meeting (first meeting after receipt of detailed grounds).	PC
5.2	Monitor timely receipt of report on assessment of detailed grounds for re-examination as well as revised version of EPMAR from rapporteur.	PC
5.3	*Following initial discussion at CVMP meeting:* Has CVMP agreed to grant an oral explanation (and when to hear it)? If **yes**, go to 5.4 If **no**, go to 5.5	
5.4	If not already done earlier in the procedure, inform applicant of date and timing of oral explanation. At least 1 week before the CVMP meeting: Monitor timely receipt of presentation and CVs of applicant representatives.	PC
5.5	At least 6 working days before the CVMP: review draft revised assessment report, draft final opinion (incl. revised EPMAR) for adoption by CVMP. Proceed to 6.0	S/CL
6.0	**Post Opinion**	
6.1	*On the last day of CVMP meeting:* finalise letter to applicant informing on the CVMP conclusions. Finalise CVMP opinion (incl. revised EPMAR) and CVMP assessment report. Send letter with opinion and assessment report to applicant via Eudralink.	PC
6.2	On the following day after the end of the CVMP meeting (usually Friday) send final opinion including revised EPMAR to the European Commission and EFTA authorities, following the steps in checklist.	PC
6.3	Check the completeness of the electronic cMF. Declare documents as a record in DREAM for the electronic cMF, if not done previously.	PC
6.4	Did the CVMP recommend provisional MRLs for the substance? If **yes**, go to 3.9 If **no**, go to 6.5	
6.5	*Within 10 days following publication of the relevant EC Regulation in the Official Journal:* Arrange for publication of EPMAR on Agency website. Proceed to 7.0	PC
7.0	**End of procedure**	

10. Records

Electronic copies are saved in the appropriately labelled folder in DREAM.

Annex I

Submission of MRL application dossiers to CVMP (published as a separate document) (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500014483.pdf)

As of 1 January 2017 it is mandatory for applicants to use the eSubmission Gateway/Web Client for all veterinary procedural submissions to the Agency. For more information, including links to guidance on registration with the system, refer to the Veterinary e-submission website: http://esubmission.ema.europa.eu/tiges/vetesub.htm.

Annex II
Standard timetable for evaluation of MRL applications

Pre-submission phase

Day	Step
-180 to -90	Notification of intent to submit an application for the establishment of MRLs
-180 to -60	CVMP plenary meeting following receipt of letter of intent Appointment of rapporteur(s) and peer reviewer; notification of recommended submission dates to applicant
-14	Submission of application dossier
0	Validation

Evaluation

Day	Step
+1	Start of assessment procedure
+70	Rapporteurs' assessment report
+120	CVMP decision on the need for further information with the adoption of a scientific overview including a list of questions
+150	Opinion, if no further information required
	If further information is required:
	Clock stop
	- 6 months timeline for submission of responses –
+121	Submission of written responses by the applicant (*clock re-start*)
+160	Rapporteurs' updated assessment report with assessment of responses to the list of questions including rapporteurs' views on need for oral or written explanations; applicant may (also) request to provide oral explanations to CVMP
+180	CVMP discussion of draft opinion *or* CVMP request for oral or written explanations on outstanding issues[7] CVMP may agree a 1-2 month clock stop to allow for preparation of oral or written explanations, if justified.
	Clock stop
+181	Oral explanation (as appropriate) (*clock re-start*)
+210	CVMP opinion

[7] Oral explanations can also be granted at the request of the applicant

Annex III
Timetable for accelerated evaluation of MRL applications

Pre-submission phase

Day	Step
-180 to -90	Notification of intent to submit an application for the establishment of MRLs, *including notification of intention to submit a request for accelerated assessment*
-180 to -60	CVMP plenary meeting following receipt of letter of intent Appointment of rapporteur(s) and peer reviewer; discuss request for accelerated procedure; if necessary request rapporteur(s) to further consider the request and advise the Committee; notification of recommended submission dates to applicant
-90 to 0	If not decided at a previous meeting, consider advice from rapporteur(s) and decide on accelerated procedure; communication of conclusions to applicant
-14	Submission of application dossier
0	Validation of dossier

Initial evaluation

Day	Step
+1	Start of assessment procedure
+45	Rapporteurs' assessment report
+90	CVMP opinion *or* CVMP expresses the need for further information (list of questions); in the latter case: *Clock stop* - 6 months timeline for submission of responses[8] –
+91	Submission of written responses by the applicant (*clock re-start*)
+115	Rapporteurs' joint assessment report including rapporteurs' views on need for oral or written explanations; applicant may request to provide oral explanations to CVMP
+119	CVMP discussion of draft opinion *or* CVMP request for oral or written explanations CVMP may agree a 1-2 month clock stop to allow for preparation of oral or written explanations, if justified.
+120	Oral explanation (as appropriate) and opinion

[8] Depending on the extent of the list of questions and the amount of data expected the CVMP might decide to revert the assessment to a standard timetable, i. e. evaluation of the responses to the list of questions in 90 days instead of 30 days.

Annex IV
Presentation of detailed grounds for request for re-examination

Requests for re-examination and supporting grounds shall contain argumentation and clarification of data previously submitted in the original application. It is not considered the purpose of a re-examination to provide an opportunity for the submission of new data.

The detailed grounds for re-examination shall be presented in one of the following ways:

a. Attached to the written notice by the applicant to the Agency secretariat of his intention to request the re-examination of the CVMP opinion (send within 15 days after receipt of the CVMP opinion).

b. Submitted separately from the written notice within 60 days of receipt of the CVMP opinion to the Agency secretariat and to CVMP members and alternates taking into account the dossier submission requirements in Annex I (addresses as per CVMP member list: http://www.ema.europa.eu/htms/general/contacts/CVMP/CVMP_members.html).

The day of the receipt is the day when the applicant receives the opinion by Eudralink. Days are counted as calendar days. The period starts at the day following the receipt of the 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.

Applicants are advised to contact the Agency secretariat before submitting the grounds for re-examination to discuss submission date and to clarify the most suitable option.

Timeline for re-examination procedure

Day 0 – 15 after receipt of CVMP opinion by Eudralink:	Applicant sends notification of request for re-examination
Next CVMP meeting:	Appointment of (co-) rapporteur for re-examination procedure
Day 0 – 60 after receipt of CVMP opinion by Eudralink:	Applicant sends detailed grounds for re-examination of CVMP opinion
First CVMP meeting after receipt of grounds:	Initial discussion at CVMP, agreement on need/granting of oral explanations
Second CVMP meeting after receipt of grounds:	Oral explanations (if applicable) Adoption of final (revised or unchanged) CVMP opinion