EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Type IB variations to centralised marketing authorisations (medicines for veterinary use)		
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1. Purpose

To describe the procedure for the handling of type IB variations to centrally authorised medicinal products for veterinary use. This SOP covers the handling of single type IB variations and groupings of type IB variations with or without type IA and IA_{IN}.

This SOP does not apply to:

- grouping of type IB (with or without type IA/IA_{IN}) with type II variations and/or extensions of marketing authorisations (refer to SOP/V/4004);
- worksharing procedures (refer to the Procedural guideline and Communication from the European Commission 2009/C 323/04).

2. Scope

This SOP applies to staff in the Veterinary Medicines Department of the Veterinary Medicines Division.

3. Responsibilities

It is the responsibility of the Head of the Veterinary Medicines department (delegated to the Service Head for Veterinary Regulatory and Organisational Support) to ensure that this procedure is adhered to within their own Department. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section *9. Procedure.*

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4. Changes since last revision

This SOP has been updated in line with revised internal procedures and organisational structure. It has been merged with SOP/V/4015 to include grouped type IB variations.

Part of section 9 relating to validation has been replaced with a validation checklist for type IB variation applications, made available as a SIAMED BI template.

5. Documents needed for this SOP

- A database and application tracking system is provided by SIAMED
- Model letters, checklists and document templates for this procedure are available in SIAMED
- Fee workflow template (EMA/461339/2014)
- Formatted table template to be inserted in application submission cover letters for veterinary procedures (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000066.jsp&mid=WC0b01ac058002da5d)

6. Related documents

- 98/C 229/03 – Commission communication on the Community marketing authorisation procedures for medicinal products
- 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
- 2013/C 223/01 – Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures (hereinafter referred to as “the Guideline”)
- Guideline on the Categorisation of Extension Applications (EA) versus Variations Applications (V), NTA, Volume 6C, October 2003
- The linguistic review process of product information in the centralised procedure – veterinary (EMA/288844/2009 Rev. 4)
- Dossier requirements for submission of marketing authorisation and maximum residue limit applications (EMA/466102/2007)
- Member States contact points for translations review (EMA/102302/2005)
- Guideline on Active Substance Master File Procedure (EMEA/CVMP/134/02) Veterinary post-authorisation guidance on type IB variations http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000057.jsp&mid=WC0b01ac058002da55

- QRD product information templates for veterinary medicines http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000185.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002d9b0
- User guide on how to generate PDF versions of the product information – veterinary (EMA/793983/2010)
- WIN/EMA/0098 – QRD forms 2 (former Linguistic Check Forms)
- Centralised procedure - Recommended submission dates (EMA/641657/2014)
- eSubmission website for veterinary submissions (http://esubmission.ema.europa.eu/tiges/vetesub.htm)
- electronic Application Form (eAF) for variations[1] (http://esubmission.ema.europa.eu/eaf/index.html)
- WIN/V/4062 - Handling of Veterinary e-submissions
- SOP/PDM/1004 – Core master files of medicinal products for human and veterinary use following the centralised procedure
- SOP/V/4038 – Updating of the European Public Assessment Report for a veterinary medicinal product

7. Definitions

Type IA variation: a minor variation, which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned, as laid down in Article 2(2) of Commission Regulation No 1234/2008 and which should be notified to the Agency within 12 months following implementation.

Type IA_{IN} variation: a minor variation, which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned. Such applications should be immediately notified after implementation to ensure continuous supervision of the medicinal product, as laid down in Articles 2(2) and 14(1) paragraph 2 of Commission Regulation (EC) No 1234/2008.

Type IB variation: a minor variation, provided that the conditions for such variation laid down in Articles 2(5) and 3(2) of Commission Regulation (EC) No. 1234/2008 are met. Variations which are neither a minor variation of Type IA nor a major variation of Type II nor an extension are classified as Type IB variation by default. Examples of foreseen Type IB variations are listed in the Guideline. Variations may also be classified as Type IB through an Article 5 recommendation procedure.

Type IB variation applications have to be assessed within 30 days following notification of positive outcome of validation. Validation is finalised within 5 Agency working days starting on the next working day after receipt of the application. In the case of an unfavourable outcome the applicant can amend the application within a further period of 30 days. After the amendment of the application (or provision of supplementary information requested) there are

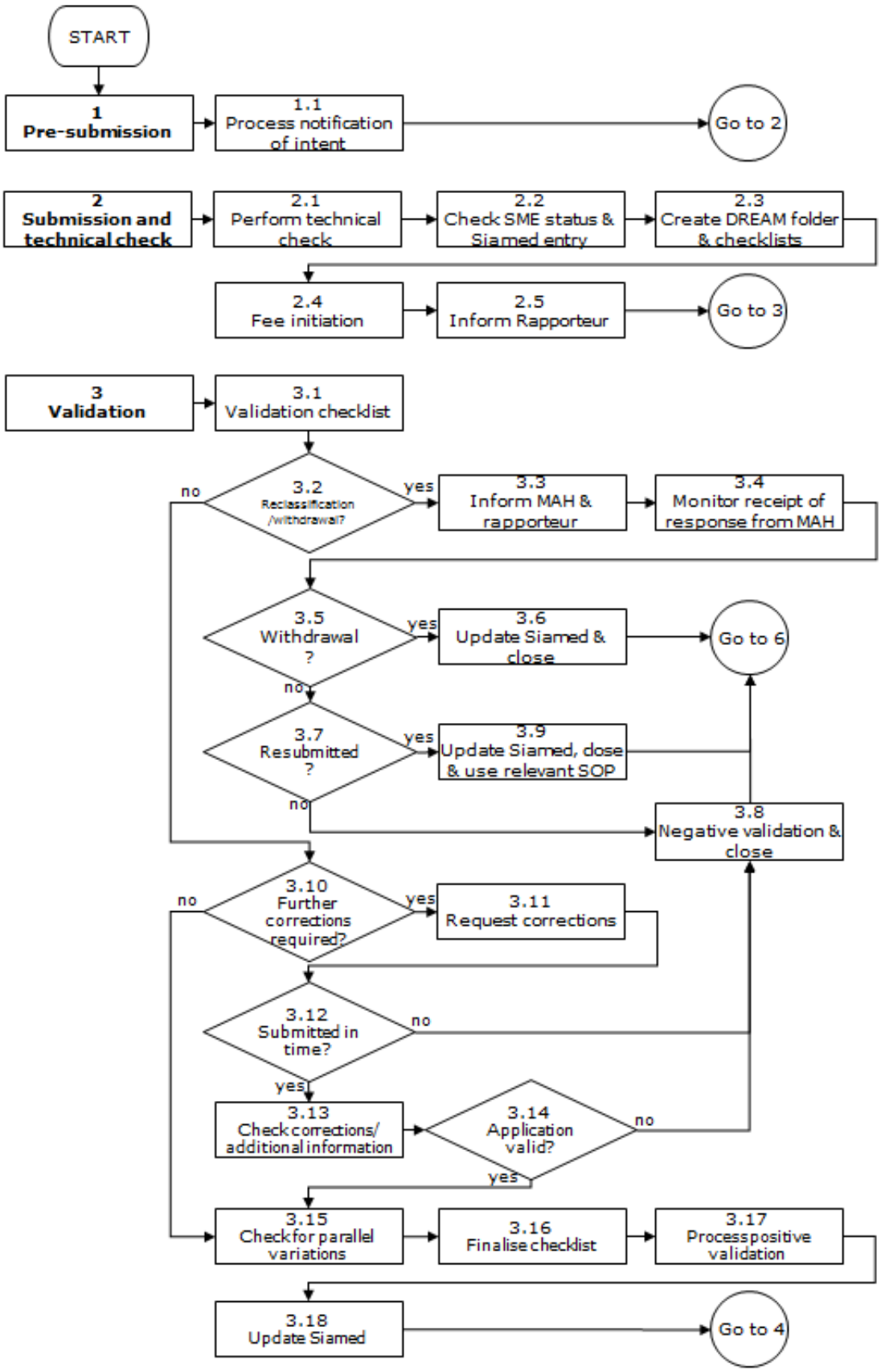
[1] The use of the eAF is mandatory from 1 July 2015 in the centralised procedure (Human and Veterinary), and from 1 January 2016 in all EU procedures (human and veterinary)

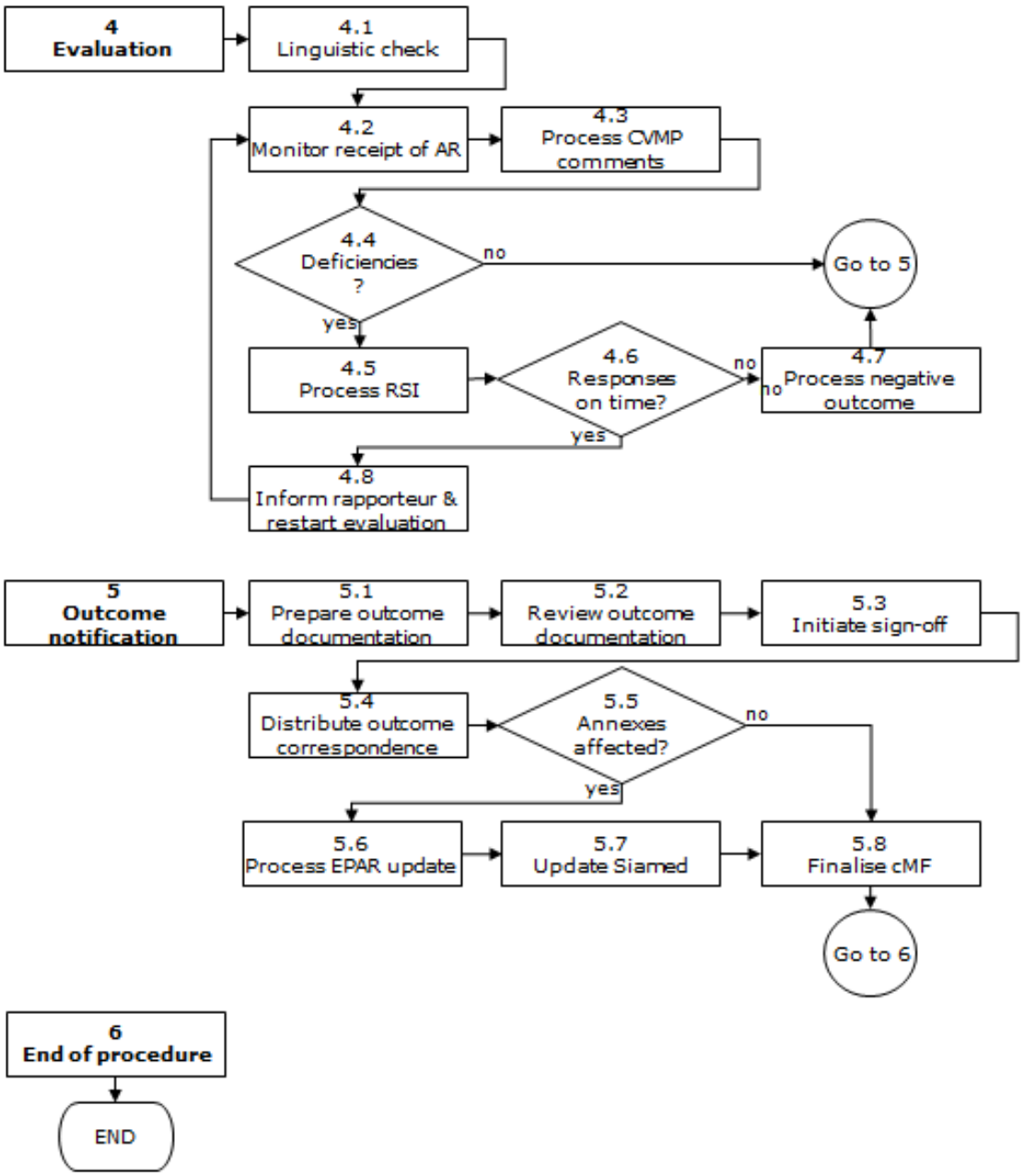
	further 30 days in which to assess the information. If following the provision of supplementary information the variation is still considered inadequately justified, this will lead to the rejection of the variation.
Unforeseen variation:	a variation is considered 'unforeseen' when the proposed variation is not considered a minor variation of Type IB following the Guideline, or has not been classified as a Type IB variation in an Article 5 recommendation. When one or more of the conditions established in the Guideline for a Type IA variation are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II.
Days:	calendar days, unless otherwise specified
VNeeS structure:	The folder structure (granularity) for an electronic veterinary submission
VNeeS checker:	The tool that checks basic parameters required for an acceptable electronic submission. VNeeS submissions can be checked against the technical validation criteria using the VNeeS checker tool. The VNeeS checker tool should be used as point of reference for technical validity of a submission by both applicants and agencies.
Technical validation:	In order to be accepted as technically valid, an electronic VNeeS submission has to comply with the common set of technical criteria defined in the 'Technical validation checklist for veterinary electronic submission' as published on the veterinary eSubmission website.
eSubmission Gateway/Web Client:	Electronic submission channel that allows secure submission over the internet

AA	Administrative Assistant (here: in V-VM-ROS; vet.applications team)
AR	Assessment Report
AST	Assistant
ClAG	Classification Advisory Group – Internal group to be consulted, when needed, in case of unclassified variations
cMF	Core Master File
CVE	Eudranet (e-mail) address for variations (All veterinary CVE)
CVMP	Committee for Medicinal Products for Veterinary Use
DDPS	Detailed Description of Pharmacovigilance System
DREAM	Document Records Electronic Archive Management
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
Eudralink	Secure mailing system for transmission of confidential documents
EURS	EXTEDO Universal Review System

E-SR-LRS	Labelling Review and Standards Office within Human Medicines Evaluation (E) Division
G-WAG	Grouping and Worksharing Advisory Group
HSer	Head of Service (here: HSer for V-VM-ROS)
MAH	Marketing Authorisation Holder
MS	Member States
P-CI	Compliance and Inspection Department within Inspections and Human Medicines Pharmacovigilance (P) Division
PI	Product Information (Summary of Product Characteristics, Labelling and Package Leaflet)
PIPIT	Translation timetable for the finalisation of the procedure
ProcM	Procedure manager appointed for the variation
QRD	Quality Review of Documents
Rapp	Rapporteur
RSI	Request for supplementary information
SIAMED	Agency database for tracking application procedures
SOP	Standard Operating Procedure
TT	Timetable
V-VM	Veterinary Medicines Department (in Veterinary Medicines Division)
V-VM-ROS	Veterinary Regulatory and Organisational Support (in Veterinary Medicines Department)
VETCOM	Eudranet (e-mail) address for the Standing Committee (All veterinary VETCOM)
WIN	Work Instruction

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




4
Evaluation
4.1
Linguistic check
4.2
Monitor receipt of AR
4.3
Process CVMP comments
4.4
Deficiencies ?
no
Go to 5
yes
4.5
Process RSI
4.6
Responses on time?
no
4.7
Process negative outcome
no
yes
4.8
Inform rapporteur & restart evaluation
5
Outcome notification
5.1
Prepare outcome documentation
5.2
Review outcome documentation
5.3
Initiate sign-off
5.4
Distribute outcome correspondence
5.5
Annexes affected?
no
yes
5.6
Process EPAR update
5.7
Update Siamed
5.8
Finalise cMF
Go to 6
6
End of procedure
END

9. Procedure

Step	Action	Responsibility
1.0	**Pre-submission**	
1.1	*Notification of intended application by e-mail to vet.applications@ema.europa.eu:* • Advise MAH to use the correct electronic variation application form; and to submit electronic "track changes" versions of product information, if applicable • Assign appropriate procedure number (*Note: the application requires the company to state this number*); and inform MAH of new EU marketing authorisation number(s) to be used, if variation creates new presentation(s) • If linguistic review is required, advise the MAH that variation should be submitted in accordance with the published recommended submission dates. • Check rapporteur availability for the intended submission date • If applicable, liaise with HSer to check if proposed grouping is acceptable. If in doubt, consult G-WAG. Inform MAH accordingly. • If new manufacturers, check with P-CI-MCP if inspection is required. Save the correspondence in DREAM product folder under "Intended applications". Proceed to 2.0	AA
2.0	**Submission and technical check (by day 2)**	
2.1	Following receipt, process application according to WIN/V/4062[2], including technical validity check. If only a hard copy was received, request an electronic version.	AA
2.2	Check the presence of the *formatted table template to be inserted in application submission cover letters for veterinary procedures*. Check if the MAH is a micro-SME company[3] – if yes, inform AST for preparation of appropriate templates. Double-check SIAMED entry and save as 'UNDER VALIDATION' (technical verification between the entry and the application form/supporting documentation).	ProcM

[2] The application is initially handled by AA appointed to monitor the mailbox
[3] SME status is declared by the MAH on the submission cover letter and should match the information about the MAH in Siamed. To find out whether it is a micro-SME (as opposed to small and medium SMEs), check the company record in the SME Database available from the EMA Intranet.

Step	Action	Responsibility
2.3	Create variation folder in DREAM under *Cabinets/01. Evaluation of Medicines/V - C/2. Active applications/[PRODUCT]/05 Post Authorisation/Post Activities*. Run a type IB validation checklist and a Core Master File checklist for type IB variations (both SIAMED BI templates) and save in DREAM. If applicable, save the translations received in DREAM 'Translations' subfolder.	ProcM
2.4	Check if Financial Workflow need to receive an email for fee initiation purposes - the latest status of when such email is required in case of type IB variations is reflected in the *email template for fee initiation* (EMA/461339/2014).	ProcM
2.5	Inform the rapporteur about the application and send a draft timetable (SIAMED BI template) by e-mail (SIAMED BI template) using the Eudranet mailbox. Proceed to 3.0	AST
3.0	**Validation (working day 1 to 4)**	
3.1	Check the submission dossier against requirements. For the details of the validation checks to be performed, refer to the Type IB validation checklist. • *If input from P-CI is required* (e.g. variations A.4, A.5, A.7, B.I.a.1, B.II.b.1, B.III.1 and C.I.8.b), send a link to the electronic submission of the variation to GXP.validation. Ask for feedback within 3 working days. *NB: for variations A.4, A.5, A.7, B.III.1 and C.I.8.b P-CI are notified only for their information and no feedback is expected.* • *In case of unclassified variations* or in case of doubt on the interpretation of the guideline, liaise with the ClAG (CLAG@ema.europa.eu) to confirm that the proposed variation can be accepted as Type IB[4]. If required, consult the rapporteur. • *If the variation applied should be an extension* (wrongly classified by MAH), request the MAH to withdraw and to follow the extension procedure. • *If the variation applied for is classified as a type II or IA(IN)* variation in the Guideline or via an Article 5 classification request (i.e. wrongly classified as type IB by MAH), reclassify the variation.	ProcM

[4] ProcM can consult the internal ClAG Database (EMA/40868/2010) of cases previously dealt with.

Step	Action	Responsibility
	To check if there has been a classification under Article 5, consult the Traffic Lights document (EMA/14987/2014) and the CMDh/v Article 5 recommendations[5]. • *If an unclassified variation or a type IB variation* which does not fully meet the description in the Guideline cannot be handled as a type IB, reclassify the variation. *NB: Always inform ClAG when you recommend a reclassification to Type II.* • *In case of grouping, check if proposed grouping is acceptable* in relation to Annex III of Commission Regulation (EC) No 1234/2008 or if it has been previously agreed. In case of doubt, consult G-WAG.	
3.2	Does the variation require reclassification or withdrawal for initiating an extension procedure? If yes, go to 3.3 If no, go to 3.10	
3.3	Inform MAH and rapporteur of the outcome by Eudralink (copied to the rapporteur's CVE Mailbox), asking MAH for confirmation within 5 working days.	ProcM
3.4	Monitor receipt of response from MAH. *NB: For reclassified variations, the MAH should provide appropriate supporting documentation (including the revised application form).*	ProcM
3.5	Was the variation withdrawn? If yes, go to 3.6 If no, go to 3.7	
3.6	Update SIAMED with request for withdrawal, mark procedure folder in DREAM as withdrawn and close the procedure. Proceed to 6.0	ProcM
3.7	Did MAH resubmit a reclassified variation application? If yes, go to 3.9 If no, go to 3.8	
3.8	Preparation of negative validation correspondence; review and submission for sign-off to HSer. Send negative validation correspondence to MAH, cc Rapporteur, ProcM and, if involved, P-CI.	ProcM AST

[5] The CMDh/v Article 5 recommendations are published on the HMA website: http://www.hma.eu/293.html

Step	Action	Responsibility
	Close the procedure in SIAMED. Proceed to 6.0	
3.9	Update SIAMED with reclassified scope and upon receipt of variation, process according to relevant SOP (SOP/V/4004 or SOP/V/4010). Proceed to 6.0	ProcM
3.10	Were any other issues identified that need to be addressed by the MAH before validation is possible? If yes, go to 3.11 If no, go to 3.15	ProcM
3.11	Send email to MAH requesting corrections to be provided within 2-3 working days (no later than 5 working days). Monitor receipt of corrections/additional information.	ProcM
3.12	Did the MAH submit within 5 working days? If yes, go to 3.13 If no, go to 3.8	
3.13	Check corrections/additional information: For the details of validation checks to be performed, refer to the Type IB validation checklist. If required, consult the Rapporteur and/or their expert. For variation(s) affecting: • A.4, A.5, A.7, B.I.a.1, B.II.b.1, B.II.b.2 and B.III.1: provide P-CI in charge of GMP aspects with the additional information (request comments within 3 working days, if applicable); • C.I.8.b: provide P-CI in charge of DDPS aspects with the additional information (request comments within 3 working days, if applicable).	ProcM
3.14	Can the application be validated considering the corrections and/or additional information provided? If yes, go to 3.15 If no, go to 3.8	
3.15	Check if any parallel variation(s) affect the annexes. If so, liaise with the relevant ProcM to coordinate product information and EPAR update. *NB: In principle, when updating the published product information/EPAR for a particular procedure, ProcM should ensure that any changes to the Annexes approved in the meantime in*	ProcM

Step	Action	Responsibility
	parallel procedures are included within the update.	
3.16	Finalise type IB checklist.	ProcM
3.17	On the last validation working day, confirm the positive validation of the application and the start date (i.e. on the next day) of the procedure by following the steps below: • Finalise the TT (ProcM to update it in SIAMED if necessary) • Prepare template for AR (SIAMED BI template) prefilled with the administrative data; • Send template for AR to the rapp (SIAMED BI template) using the rapp's CVE Mailbox • Inform CVMP members by e-mail (CVE mailbox) about the validation and include TT (SIAMED BI template) • Inform the MAH by Eudralink (SIAMED BI template) about the outcome of the validation and the start date of the procedure (including TT, unless the recommended submission dates for procedures requiring linguistic review are followed) • If applicable, inform QRD Secretariat of the upcoming linguistic review and send translations PIPIT (e-mail to E-SR-LRS) • Send fee initiation email to Financial Workflow, if required (using the template).	AST
3.18	Update SIAMED with validation outcome and any relevant information which has been changed as a result of validation. Proceed to 4.0	ProcM
4.0	**Evaluation**	
4.1	For variations requiring linguistic check: Ensure that the MAH has submitted the revised PI in all languages to the Member States by e-mail according to the PIPIT provided (by day 5). Monitor and save the MS linguistic comments in DREAM. *NB: Refer to the 'Linguistic review process of product information in the centralised procedure and member states contact points for translations review'. In cases where the PI is affected and linguistic review is required, the variations should be submitted in accordance with the published recommended submission dates.*	AST
4.2	By day 20 Monitor receipt of AR and ensure its timely circulation to the Agency and All Veterinary CVE.	ProcM

Step	Action	Responsibility
	Upon receipt of the AR record the expected outcome in SIAMED.	
4.3	By day 25	
	Check if any comments have been sent from CVMP members to the rapporteur and the Agency. If comments are not in agreement or additional proposals are made, liaise with rapporteur to revise the AR by day 28.	ProcM
	Save comments received in DREAM.	AST
	If applicable, ensure receipt of all final translations from the MAH with [formatted] annexes as required for EPAR publishing (SOP/V/4038) and conforming to the Agency's user guidance on PDF versions.	AST
4.4	Have deficiencies in the application been identified by the rapporteur/CVMP members? If yes, go to 4.5 If no, go to 5.0	
4.5	By day 30	
	Prepare correspondence for request for supplementary information (RSI).	AST
	Review RSI correspondence and submit for sign-off.	ProcM AST
	Send to MAH by Eudralink (include the draft AR), allowing the MAH a further 30 days to reply.	
4.6	Were responses to RSI received within 30 days? If yes, go to 4.8 If no, go to 4.7	
4.7	RSI response not received: prepare negative outcome notification. Proceed to 5.0	AST
4.8	Inform the rapporteur by e-mail, using the rapporteur's CVE Mailbox and update TT with relevant administrative data. *Note: Day 1 of the second evaluation period starts on the day after receipt of the MAH responses.* Proceed to 4.2	AST
5.0	**Outcome notification**	
5.1	Generate from SIAMED the templates for the notification of outcome (positive, negative or combination of positive and negative, as applicable). • For *grouped variations*, list clearly all favourable and	AST

Step	Action	Responsibility
	unfavourable variations in the notification, as applicable. • If the *grouping includes type IA quality scopes* with an unfavourable outcome due to the fact that the conditions for type IA variation(s) are not met and consequently a resubmission (as a type IB or type II variation or extension of MA) is needed: - Inform P-CI of the negative outcome of the variation. - In outcome correspondence, include the sentence: "*According to Art 24(1) of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder is reminded that the holder should cease to apply the variations with an unfavourable outcome immediately after receipt of this letter. Moreover, the MAH should follow the quality defect procedure in case of a suspected quality defect.*" *NB: The MAH has to follow the instructions on the Product Defects web page.* • If *linguistic check* took place, fill in section 2 of the QRD Form 2 and send it to QRD Secretariat via e-mail to E-SR-LRS (see WIN/EMA/0098). • If *Annexes are affected*: For the EPAR update, create in DREAM a new sub-folder called 'Final PI' under: [Product]\05 Post-Authorisation\Post Activities\[relevant variation folder] where the annexes will be saved (Word document with track changes and clean PDF). Provide link(s) to correspondence in DREAM to ProcM for checking.	
5.2	Review documents and SIAMED entry and inform AST when done.	ProcM
5.3	Once correspondence is reviewed in DREAM, prepare and circulate a signature book with a sign-off cover page containing: • the notification type IB or notification of rejection type IB and the amended annex(es) in EN only (if applicable). In case that many/all presentations are affected, include only one example; • Notification letter to MAH; • Notification Eudralink to MAH; • E-mail to All Veterinary CVE (copy to P-CI, if involved in the procedure); • If Annexes are affected: - Notification Eudralink to EC; - E-mail to ENTR-V-VETCOM; Provide the ProcM with the signature book for review and signature.	AST

Step	Action	Responsibility
5.4	Once documents have been signed off, distribute correspondence, as applicable. Update the entry in SIAMED which is affected by the favourable variation, e.g. manufactures, contact persons, list of presentations or presentations details, etc. Record the scientific summary. Finalise procedure in SIAMED – set the status of the outcome as final. *NB: The summary text should read, for example, "The (European Medicines) Agency accepted the variation to <shortened text from the precise scope>". This will appear on the "Steps taken after authorisation" document published on the Agency website.*	AST ProcM
5.5	Does the variation affect the Annexes? If yes, go to 5.6 If no, go to 5.8 *NB: If this variation does not affect the Annexes, it will need to be mentioned on the "Steps taken after authorisation" document with the next variation affecting the Annexes.*	
5.6	Process EPAR update following SOP/V/4038. *NB: If there are any parallel variations affecting the Annexes, liaise with colleagues to include all changes in one EPAR revision (all procedures must be final).*	AST
5.7	After EPAR publication: record the EPAR revision details in SIAMED.	AST
5.8	Save the main procedure documents in DREAM variation folder, including relevant correspondence with MAH and different Agency services involved, and add to core Master File the documents required by the cMF checklist in accordance with SOP/PDM/1004. Proceed to 6.0	ProcM
6.0	**End of procedure**	

10. Records

The electronic submission including cover letter, application form, the full variation dossier and revised submissions (where requested) are stored in the EURS repository at the Agency.

Amended Annexes (if applicable) are saved in DREAM in the procedure folder, in its subfolder "Translations".

Electronic versions of acknowledgments of receipt (where applicable), scanned copies of all signed correspondence, relevant emails to the MAH and Rapporteur (if necessary) are saved in DREAM in the procedure folder.

Paper copies of all other correspondence related to the procedure should be stored in temporary filing area by their date of submission/issue and discarded after 6 months have elapsed for the date of issue/submission.

The crucial procedure documents are to be saved in DREAM product folder and declared as records for long preservation by adding them to the electronic cMF, in accordance with SOP/PDM/1004 and the cMF checklist applicable to the procedure.