21 November 2017
EMA/503274/2017
Veterinary Medicines Division

Questions & answers on Article 13 referral procedures

This guidance document addresses a number of questions which stakeholders, in particular the marketing authorisation holders (MAHs), may have on Article 13 referral procedures to the Committee for Medicinal Products for Veterinary Use (CVMP). It provides an overview of the European medicines Agency's ('the Agency') practical and operational aspects with regards to handling of Article 13 referral procedures.

This integrated version has been created for printing purposes only. Please refer to the individual questions & answers as published in the referral procedures guidance to access the hyperlinked information.

Questions & answers are being updated continuously, and will be marked by 'NEW' or 'Rev.' with the relevant date upon publication.

Note:

It should be highlighted that this document has been produced for guidance only, and should be read in conjunction with "The Rules governing Medicinal Products in the European Union, Notice to Applicants", Volume 6A, Chapter 3.

Marketing authorisation holders must in all cases comply with the requirements of EU legislation.

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

Table of contents

Initiation of Article 13 referral procedure

1. What is the legal basis for an Article 13 referral procedure?

An Article 13 referral procedure follows the provisions of Article 13(1) of Regulation (EC) No 1234/2008.

It applies when, during the co-ordination group procedure carried out by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv), the Member States fail to reach an agreement under the mutual recognition/decentralised procedure on a major variation of Type II or on a worksharing variation procedure, on the grounds of a potential serious risk to human or animal health or to the environment.

The procedure for an Article 13 referral is laid down in Articles 33(3), (4) and (5) of Directive 2001/82/EC for which the procedure described under Articles 36, 37 and 38 of Directive 2001/82/EC is applied.

References:

Commission Regulation (EC) No 1234/2008

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

Notice to Applicants, volume 6A Procedures for marketing authorisation, Chapter 3 Union Referral Procedures

Guideline on the definition of a potential serious risk to human or animal health or to the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC

2. In which situations can an Article 13 referral procedure be initiated?

An Article 13 referral procedure should be initiated on the grounds of potential serious risk to human or animal health or to the environment, where no agreement has been reached by the Member States during the 60-day referral procedure carried out by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) with respect to:

- Recognising the decision on a major variation of Type II within 30 days, with reference to Article 10(4) of Commission Regulation (EC) No 1234/2008 or;
- Approving an opinion on a worksharing variation procedure within 30 days, with reference to point (b) of Article 20(8) of Commission Regulation (EC) No 1234/2008.

In such a case the reference Member State will refer the matter to the Agency based on the concern(s) raised by the objecting concerned Member State(s). A concern regarding potential serious risk to human or animal health or to the environment may only be raised by a concerned Member State in case the overall assessment of the variation by the reference Member State is positive.

For the definition of 'potential serious risk to human or animal health or to the environment', the Commission has adopted a guideline and annex of examples (please refer to Guideline on the definition of a potential serious risk to human or animal health or to the environment and annex).

References:

Commission Regulation 1234/2008

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

Notice to Applicants, volume 6A Procedures for marketing authorisation, Chapter 3 Union Referral Procedures

3. Who can initiate an Article 13 referral procedure?

An Article 13 referral procedure must be initiated by the reference Member State when its assessment is positive but the concerned Member States do not reach agreement in the co-ordination group's referral procedure based on identification of grounds constituting a 'potential serious risk to human or animal health or to the environment'.

The reference Member State shall provide the notification form for a referral procedure to the Committee for Medicinal Products for Veterinary Use (CVMP)/Agency, which will include a detailed statement of the matter(s) on which the Member States concerned have been unable to reach agreement and the reasons for the disagreement, based on grounds of potential serious risk to human or animal health or to the environment.

References:

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

Notice to Applicants, volume 6A Procedures for marketing authorisation, Chapter 3 Union Referral Procedures

4. Can the variation application be withdrawn before the initiation or during an Article 13 referral procedure?

A variation application may be withdrawn by the marketing authorisation holder (MAH) at any time in any Member State.

However, after a concern for potential serious risk to human or animal health or to the environment has been raised in accordance with Article 13 of Commission Regulation (EC) No 1234/2008 by a concerned Member State, a withdrawal of the variation application in some of the Member States will not stop the matter from being discussed within the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) and, eventually, from a referral procedure being initiated at CVMP level.

The referral procedure can only be stopped if the MAH withdraws the variation application in all the European Economic Area (EEA) Member States.

5. Which veterinary medicinal products can be involved in an Article 13 referral procedure?

For Article 13 referral procedures, only the concerned veterinary medicinal product(s) for which a variation to national marketing authorisations has been applied for, either under the mutual recognition/decentralised procedure or via a worksharing procedure, will be the subject of the referral.

The marketing authorisation holder (MAH) will be requested to provide a list of the (invented) names of the veterinary medicinal product(s), the name of the MAH to whom the product(s) is/are authorised, the strength(s), pharmaceutical form(s), route of administration(s), target species in the respective

Member States. This will be checked by the EMA with the national competent authorities of the Member States.

6. Should the marketing authorisation holder identify a contact person to communicate with the Agency during the Article 13 referral procedure?

To facilitate the exchange of information prior to the start and during the procedure, the marketing authorisation holder (MAH) should confirm the designated contact person for the Article 13 referral procedure by way of a letter of representation.

All documentation concerning the Article 13 referral procedure will be sent to the contact person only. The contact details of the person should be clearly stated (name, address, phone and fax number and email address) in the letter of representation.

The MAH may, if they wish, be represented by another party (e.g. a consultant), who will be the contact person for the procedure. In this case the MAH must inform the EMA's procedure coordinator identified in the letter that is sent to the MAH when the referral procedure is initiated.

It is the responsibility of the MAH to notify the Agency of any change that might affect the validity of the letter of representation as soon as possible (e.g. in case of a change of the contact person), and to provide a revised letter of representation in such cases. Receipt of any documents by the contact person will be considered to constitute effective receipt by the MAH *inter alia* for the purposes of calculating the procedural timelines.

7. When and how will the start of the Article 13 referral procedure be announced?

The matter will be discussed at the next upcoming plenary meeting of the Committee for Medicinal Products for Veterinary Use (CVMP) and a brief summary will be included in the respective agenda published at the beginning of that CVMP meeting.

The start of the procedure will be announced as part of the CVMP meeting highlights, which will be published on the next working day following the CVMP meeting during which the matter is considered.

The announcement will specify the concern under consideration in general terms.

8. How will the marketing authorisation holder be informed about the start of the Article 13 referral procedure?

The marketing authorisation holder (MAH) of the product concerned by the Article 13 referral will be notified electronically (via e-mail/Eudralink) by the Agency. The letter notifying the MAH of the procedure initiation will include:

- the name and contact details of the Agency's dedicated procedure coordinator for the referral who will be the primary contact point during the procedure, as well as the e-mail address of the referral procedure-shared mailbox, which should always be copied in all correspondence with the Agency;
- the notification triggering the referral procedure;
- the timetable and the list of questions (see Question 10 below) adopted by the Committee for Medicinal Products for Veterinary Use (CVMP).

9. Does the marketing authorisation holder have to pay a fee?

No fees are payable for referral procedures under Article 13 of Commission Regulation (EC) No 1234/2008.

10. Who can submit data to be considered during the Article 13 referral procedure?

As soon as the marketing authorisation holder (MAH) for the concerned product(s) is informed that a matter concerning a potential serious risk to human or animal health or to the environment has been referred to the Agency, the MAH must forward to the Agency a copy of the variation application submitted to the competent authorities of the Member States concerned, as referred to in Article 10(1) and (3) or 20(3) and (6) of Commission Regulation (EC) No 1234/2008.

At the start of the Article 13 procedure, the MAH will be requested to submit further information relevant for the assessment, in response to a list of questions adopted by the Committee for Medicinal Products for Veterinary Use (CVMP).

This is an opportunity for the MAH to present written and/or oral explanations to the CVMP within a time-limit as specified in the procedure timetable, before an opinion is issued by the CVMP.

The MAH will be informed of the start of the procedure and during the procedure on how and when to submit data (please refer to Questions 8, 11 and 14).

Regardless of whether or not the MAH presents explanations to the CVMP, an opinion will be issued by the CVMP, applicable to all marketing authorisations concerned by the procedure.

11. How will data be gathered during the Article 13 referral procedure?

At the start of the procedure, the data considered necessary for the assessment will be identified in a list of questions for submission within the specified deadline as indicated in the timetable (please refer to Questions 8, 14 and 15).

The Committee for Medicinal Products for Veterinary Use (CVMP) may also collect additional data from the marketing authorisation holder through a list of outstanding issues and/or in an oral explanation as specified in the procedure timetable.

The CVMP may also take into account any other information at its disposal which relates to the quality, safety and efficacy, as appropriate, of the veterinary medicinal product(s) concerned and which may help in arriving at its opinion.

12. Who will perform the assessment?

The assessment of data within the Article 13 referral procedure is the responsibility of the Committee for Medicinal Products for Veterinary Use (CVMP). At the start of the procedure, the CVMP Chairperson appoints a rapporteur and (co-)rapporteur who will perform the assessment of all data collected within the agreed timelines.

The assessment of all the available data will result in the CVMP adopting an opinion on the issue reviewed.

13. How are the rapporteur and co-rapporteur appointed?

At the next upcoming CVMP plenary meeting, the Chairperson of the Committee for Medicinal Products for Veterinary Use (CVMP) appoints (co-)rapporteurs for an Article 13 referral procedure from amongst the members or alternates.

The CVMP Chairperson will appoint the rapporteur and co-rapporteur to represent the objecting concerned Member State and reference Member State, respectively.

Reference:

Appointment and responsibilities of the rapporteur and co-rapporteur for procedures regarding veterinary medicinal products

During the assessment

14. How shall I present my answers to the CVMP's list of questions/outstanding issues?

The marketing authorisation holder (MAH) is requested to submit all available evidence to support the Article 13 referral procedure to the Agency and all members of the Committee for Medicinal Products for Veterinary Use (CVMP).

It is left to the MAH's discretion to submit the relevant documentation necessary for the evaluation of the matter referred.

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAH and is crucial to the overall assessment. All submissions are expected to be submitted in English and electronically only.

The answers should be numbered according to the numbering on the CVMP list of questions or list of outstanding issues. The answers should be presented in two parts as described below:

Section I

Section I should contain an introduction, a written summary answering each question, a conclusion and a proposed summary of product characteristics/labelling/package leaflet (if requested).

The MAH is requested to provide a table of contents listing all the studies referred to in the answers. For published studies, reference to the publication should be made; for each unpublished study (e.g. proprietary data), a clear statement should be provided indicating whether a detailed description of the study and its results cannot be released to the public in accordance with the relevant principles of law governing transparency and the protection of commercially confidential information. The MAH should be aware that a brief summary of each study may nevertheless be included in the overall summary of the assessment, which will be published.

Section II

Section II should contain the supportive documentation (e.g. protocols, study reports, literature) organised by quality, safety, residue, pre-clinical and clinical data and post-marketing experience, as applicable.

In response to a specific question, proprietary or published data may be presented.

15. To whom shall I submit my answers?

Responses from the marketing authorisation holder (MAH) should be submitted to the rapporteur, the co-rapporteur, all remaining members of the CVMP (including co-opted members) and to the Agency within the timeline specified in the cover letter to the list of questions or list of outstanding issues.

All submissions for referral procedures should be sent to the Agency via the eSubmission Gateway or eSubmission Web Client. These portals send automated acknowledgement of receipt of submission, or of failed submission if an error occurred. The Agency no longer accepts submissions on CD-ROM or DVD.

For detailed information on submission to CVMP members please refer to the dossier requirements for referral procedures.

For more information please refer to eSubmission website.

There is no need to send any separate paper cover letters for these submissions.

Should you have any questions regarding your submission, please contact us via email: vet.applications@ema.europa.eu, for any technical issues contact eSubmission@ema.europa.eu.

16. How will my data be assessed?

All information gathered will be assessed within an agreed timeframe (please refer to Question 17). The assessment report(s) prepared by the CVMP (co-)rapporteurs will reflect all data reviewed and considered relevant for the assessment.

The CVMP may in some cases require input from other individual experts to advise it on specific questions in relation to the assessment.

The CVMP (co-)rapporteur's assessment report(s) will be circulated to the CVMP members for comments.

17. What is the timetable for the assessment by the CVMP?

Please note that the timelines below are provided for guidance purposes only and they refer to active days, which correspond to the time the Committee for Medicinal Products for Veterinary Use (CVMP) takes to assess the data provided.

The timetable for the Article 13 referral procedure is as follows:

Article 13 referral procedure - *Timetable for the assessment*	Active day
Notification of a referral procedure to the CVMP/Agency Secretariat	Day 0
Discussion at the first meeting of the CVMP following receipt of the notification: • Appointment of the (co-)rapporteurs • Discussion of the question(s) referred • Adoption of a timetable and CVMP list of questions to be addressed by the marketing authorisation holder (MAH)	Day 1
Preparation and submission of written explanations by the MAH in response to the CVMP list of questions	Clock Stop

Article 13 referral procedure - *Timetable for the assessment*	Active day
Re-start of the procedure following submission of written explanations	Clock re-start Day 2
Circulation of the (co-)rapporteur's assessment report(s) on the MAH's written responses and on the proposed summary of product characteristics (SPC)/labelling/package leaflet, if applicable	Day 20
Comments in writing from CVMP members on the (co-)rapporteur's assessment report(s) and proposed SPC/labelling/package leaflet, if applicable	Day 25
Discussion at the CVMP meeting: • Discussion of assessment report(s) and comments received from CVMP members; • Decision on need for oral explanations; • Adoption of a CVMP list of outstanding issues to be answered in writing and/or in an oral explanation, if needed.	Day 30
Preparation and submission of written and/or of oral explanations by the MAH in response to the CVMP list of outstanding issues, if applicable	Clock Stop
Re-start of the procedure following submission of written explanations or at the time of oral explanations	Clock re-start Day 31
Circulation of the (co-)rapporteur's revised assessment report on the MAH's explanations and on the proposed SPC/labelling/package leaflet, if applicable	Day 45
Adoption of a CVMP opinion (with annexes as provided in Article 36 of Directive 2001/82/EC) and CVMP assessment report	Day 60

The CVMP may, however, suspend the time limit of 60/150 days (clock-stop) in order to allow the MAH to prepare the responses to the CVMP list of questions, list of outstanding issues or for an oral explanation (as appropriate).

As a general rule, a clock-stop of up to three months will apply. For an extension of the clock-stop, the MAH should send a justified request to the Agency for agreement by the CVMP. The letter specifying the length of the requested extension should be addressed to the CVMP Chairperson, signed and sent electronically to the EMA's procedure coordinator. In preparing the justification, the MAH should consider the issue under consideration and the impact the extension may have. The CVMP will consider the request, and if agreed, a revised timetable will be adopted.

18. Will I receive the CVMP (co-)rapporteur's assessment report(s)?

The marketing authorisation holder (MAH) will be provided with the Committee for Medicinal Products for Veterinary Use (CVMP) (co-)rapporteur's assessment report(s) electronically via Eudralink.

19. Will I have the possibility to present my views in front of the CVMP and how is this organised?

The Committee for Medicinal Products for Veterinary Use (CVMP) may decide whether there are issues that would benefit from being addressed orally by the marketing authorisation holder (MAH). The MAH will be duly informed in advance of the issues to be addressed during an oral explanation.

The MAH may also make a request to the CVMP to present an oral explanation. In such a case, the MAH should send a written request to the CVMP Chairperson (via the EMA's procedure coordinator), stating the reason(s) and specifying the issue(s) to be addressed during the oral explanation. The CVMP will consider the request and will decide whether the oral explanation may be held.

The oral explanation should take place during the assessment phase and after the receipt of the CVMP (co-)rapporteur's assessment report(s). Further detailed information on organisational aspects of the oral explanation can be found here.

20. What should I do if my veterinary medicinal product is withdrawn or transferred to another marketing authorisation holder?

If a marketing authorisation is withdrawn in any Member State during the referral procedure, the former marketing authorisation holder (MAH) should inform the EMA's procedure coordinator for the referral procedure without delay. The Agency will then liaise with the national competent authority of the Member State concerned. Following confirmation by the national competent authority of the withdrawal of the marketing authorisation, the Agency will inform the former MAH that this specific marketing authorisation will no longer be included in the ongoing referral procedure.

If the marketing authorisation is transferred during the referral procedure, the new MAH should provide a copy of the transfer decision of the relevant competent authority to the procedure coordinator for the referral procedure. It should also provide information on the new contact person for the procedure to the procedure coordinator (please refer to Question 6). Following receipt of the transfer decision, the Agency will inform the former MAH that they are no longer included in the referral procedure, in relation to the marketing authorisation transferred.

21. What should I do if the name of my veterinary medicinal product changes or if the name or address of the marketing authorisation holder changes?

If the name of the veterinary medicinal product or the name and/or address of a marketing authorisation holder (MAH) changes during the referral procedure, the MAH should inform the EMA's procedure coordinator. The Agency will then liaise with the national competent authority of the Member State(s) concerned. Following confirmation by the national competent authority of the change, the Agency will inform the MAH that the change has been noted.

Committee for Medicinal Products for Veterinary Use (CVMP) opinion

22. When will the CVMP opinion be issued?

The Committee for Medicinal Products for Veterinary Use (CVMP) will issue an opinion on the matter within the agreed timeframe (please refer to Question 17). The CVMP opinion will usually be adopted on the last day of the CVMP's plenary meeting.

23. What could be the opinion of the CVMP?

The Committee for Medicinal Products for Veterinary Use (CVMP) opinion on an Article 13 referral procedure may be that:

a) the marketing authorisations should be varied, and/or;

b) the marketing authorisations should be varied subject to certain conditions;

c) the variation application does not satisfy the criteria for approval and should be rejected.

In the case of a positive outcome of the referral procedure resulting in the variation of the marketing authorisations, an amended summary of product characteristics, labelling and package leaflet will be annexed to the CVMP opinion, if applicable. It is also possible that the assessment of the CVMP concludes that no modifications of the final versions of the summary of product characteristics, labelling and package leaflet achieved during the co-ordination group procedure are needed, in which case the CVMP opinion shall reflect that conclusion.

In cases where the assessment of the CVMP is restricted to limited parts of the summary of product characteristics, labelling and package leaflet, only those parts which were subject to amendment during the referral procedure will be annexed to the CVMP opinion, together with a statement that, for the remaining parts, the summary of product characteristics, labelling and package leaflet are the final versions as achieved by the end of the co-ordination group procedure.

Where the variation is approvable subject to certain conditions, these will be clearly stated in the CVMP opinion. Conditions to the marketing authorisation can include, but are not limited to, requesting the marketing authorisation holder to conduct a post-authorisation study. The assessment of the fulfilment of the condition(s) will be the responsibility of the Member States, coordinated by the reference Member State unless otherwise stated.

The CVMP opinion can be adopted by consensus or by majority vote. In the event of an adoption by a majority vote, the divergent positions of the relevant CVMP members will be appended to the opinion.

24. How is the CVMP opinion structured?

The Committee for Medicinal Products for Veterinary Use (CVMP) opinion will include:

- a cover page in which the adopted opinion is outlined together with the voting outcome of CVMP;
- a listing of all veterinary medicinal products concerned, including the names of all identified products involved in the procedure and their respective marketing authorisation holders (MAHs) in each Member State;
- the scientific grounds and explanations for the CVMP opinion;
- the summary of product characteristics/labelling/package leaflet, or those parts which were subject to amendment during the referral procedure, if applicable;
- the conditions or restrictions imposed on the marketing authorisation(s), if applicable;
- any divergent views of CVMP members, in case the opinion is adopted by majority;
- the CVMP assessment report on the evaluation of all the data submitted and the conclusion of the CVMP that led to the adoption of the opinion.

25. When is the CVMP opinion published?

A brief outcome of the Committee for Medicinal Products for Veterinary Use (CVMP) opinion will be included in the CVMP meeting highlights that are released on the Friday of the CVMP plenary meeting week.

A Questions & Answers document and all annexes of the CVMP opinion will be published on the Agency's website following the adoption of the European Commission Decision (please refer to Question 30).

26. Will I receive the CVMP opinion?

The designated contact person representing the marketing authorisation holder (MAH) (please refer to Question 6) identified at the start of the procedure, will receive the Committee for Medicinal Products for Veterinary Use (CVMP) opinion and assessment report following their adoption.

27. When and how can I request a re-examination of the CVMP opinion?

The marketing authorisation holder (MAH) may, within 15 calendar days of the receipt of the Committee for Medicinal Products for Veterinary Use (CVMP) opinion, notify the Agency in writing of its intention to request a re-examination of the CVMP opinion. The request must be submitted via email to vet.applications@ema.europa.eu within the stated timeline.

In case this deadline is not respected, the request for re-examination is considered inadmissible and the CVMP opinion becomes final and will be sent to the European Commission for the initiation of the decision-making process.

Re-examination

If, within 15 calendar days of receipt of the CVMP opinion, the MAH has notified the Agency in writing of its intention to request a re-examination of the CVMP opinion, the Agency will inform the CVMP and new CVMP (co-)rapporteurs will be appointed for the re-examination procedure.

The detailed grounds for the re-examination requested should be sent to the Agency within 60 calendar days of receipt of the CVMP opinion. The detailed grounds for re-examination must be sent within the stated timelines. In case these deadlines are not respected, the request for re-examination is considered inadmissible and the CVMP opinion becomes final.

The detailed grounds submitted will determine the scope of the re-examination procedure and may encompass all aspects set out in the CVMP opinion or only certain aspects of it. However, no new data can be presented and considered at this stage of the procedure.

The re-examination procedure will only deal with the aspects of the CVMP opinion identified by the MAH in the detailed grounds for re-examination. The MAH may request that the CVMP consults a scientific advisory group (SAG) or ad-hoc expert group (AHEG) during the re-examination procedure. In such a case, this request should be made as early as possible, and should be no later than the submission date of the detailed grounds.

Within 60 calendar days of receipt of the detailed grounds for re-examination, the CVMP will conclude its assessment of the detailed grounds and adopt a final opinion.

The CVMP final opinion following re-examination will be sent to the European Commission for the initiation of the decision-making process.

28. When do I have to submit translations?

The marketing authorisation holder (MAH) will have to provide translations in all EU languages (including Icelandic and Norwegian, if applicable[1]) of the following annexes to the Committee for Medicinal Products for Veterinary Use (CVMP) opinion:

- listing of veterinary medicinal products concerned by the procedure;
- the summary of product characteristics/labelling/package leaflet or those parts which were subject to amendment during the referral procedure, if applicable.

The Agency will contact the MAH as early as possible to ensure the smooth running of the process.

Detailed information on the translation process of the CVMP opinion will be included in the letter notifying the adoption of the CVMP opinion.

29. What happens after the final opinion of the CVMP on the Article 13 referral procedure?

Following receipt of the CVMP opinion and after the translation process has been finalised, the European Commission will start the decision-making process leading to the adoption of a binding decision addressed to the Member States and notified to the marketing authorisation holder (MAH).

Detailed information on the decision-making process can be found here.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) recommendation for implementation of Commission Decisions can be found here.

30. Will there be any publication in relation to the Article 13 referral procedure after the European Commission Decision?

Around four weeks after the adoption of the European Commission Decision, a Questions & Answer document summarising the subject and outcome of the referral procedure, as well as all annexes of the CVMP opinion in all EU languages, will be published on the Agency's website.

[1] If authorised in Iceland and Norway