EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 January 2024
EMA/CHMP/CVMP/QWP/5/2024
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)

QWP Questions and Answers (Q&A): how to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV)

1. Introduction

The CEP procedure[1, 2] is widely used in EU for submission of pharmacopoeial active substance manufacturer data. Based on experience gained by National Competent Authorities (NCA) and the extensive use of CEPs in MAA/MAV, it has become apparent that some aspects of Marketing Authorisation Holders (MAH)/applicant responsibilities need to be elucidated.
This document aims to clarify existing guidance as a compilation of required data to be submitted in a MAA or in certain MAVs when a CEP is referred to in the MA dossier. It is also applicable when an excipient covered by a CEP is used as an active substance (AS).
Even if several aspects of this document would equally apply to ASMFs and when full information on active substance is provided in the MA dossier, the focus of this Q&A is on CEPs.

2. Summary of MAH/Applicant responsibilities

MAHs are responsible for the quality, safety and efficacy of medicinal products they place on the market throughout their lifecycle. Therefore, the level of knowledge of the MAH/applicant in relation to manufacture and controls of the API should be such that it permits them to take responsibility for the quality of the active substance as incorporated into the finished product, irrespective of the way this is documented in the dossier (i.e. full information in MA dossier, ASMF or CEP)[3]. It is therefore expected that when a CEP is referred to in a dossier, the MAH/applicant has access to detailed information equivalent to the open part of an ASMF via suitable technical agreements[4, 5]. This detailed information should not be included in the dossier; rather, it should be documented in the MAH/applicant's quality system (PQS). Any additional aspects not covered by the CEP, but relevant to a specific finished product, should be addressed by the applicant including further information on the intended use (of substance). The applicant should generate and submit this information in module 3[4]. Timely

[1] Directive 2003/63/CE section 3.2. (7)
[2] Commission delegated regulation (EU) 2021/805
[3] Reflection paper on GMP and marketing Authorisation Holders (EMA/419517/2021), January 2022, version 2, section 5.3.
[4] Lessons learnt from presence of N-nitrosamine impurities in sartan medicines, overview and recommendations, EMA/526934/2019, (see in particular pages 4 of the overview and 41-42 of the technical background)
[5] Guideline on Active Substance Master File Procedure, CHMP/QWP/227/02 Rev 4/ Corr *; EMEA/CVMP/134/02 Rev 4/ Corr *, Annex I).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

cooperation and communication between applicants and their CEP holders are essential, including when changes are made by the CEP holder [4, 6].

3. Information to be included in the MA application/dossier

The following Q&A clarify the additional information and supporting data that are not necessarily addressed in the 'Guideline on Summary of Requirements for active Substances in the Quality Part of the dossier, 'CHMP/QWP/297/97 Rev 1 corr' and EMEA/CVMP/1069/02' in force since 2005 and the EU Variation classification guideline[7, 8] and other relevant guidance[9].

3.1. Should a QP (qualified person) declaration be submitted when a CEP is used as the means of submission of data on the active substance in a MAA or MAV and which are the sites to be included in? (QP in Module 1/ VNees Part 1)

A valid QP declaration[10] is required by the MAH/applicant to attest that manufacturing of the active substance is performed according to the detailed guidelines on Good Manufacturing Practices for starting materials as adopted by the Community. In the case of a CEP, the QP declaration should mention all the sites involved in the manufacturing process of the active substance (including sites of manufacture of intermediates and those performing any physical treatment of the active substance such as micronisation, lyophilisation). If a CEP does not cover a specific grade i.e. a grade not assessed by EDQM or not submitted/claimed in the CEP dossier, still the site where the physical treatment is performed should be audited and mentioned in the QP declaration.

The MAH/applicant should be aware of the whole manufacturing chain of the active substance after introduction of the active substance starting materials. Therefore, the QP declaration should include all the sites actually used in the manufacturing process of the active substance regardless of whether they may be mentioned on the CEP or in its annex[11].

In case a CEP mentions more than one manufacturing sites performing complete manufacture of the AS but the finished product manufacturer (FPM) uses only AS material from one manufacturing site only the AS site actually used would be subject to QP declaration under certain conditions as reported in the relevant CMD Q&A on QP declaration[12] (Q&A 5).

3.2. What standard information should be submitted in CTD sections 3.2.S / 3.2.R or VNees Part 2C of the MA dossier? (Module 3, subsections of S)

A copy of the most recent version of the CEP with the declaration of access to the MAH/ applicant on the CEP or a Letter of access for CEP 2.0 duly filled and signed should be included in section 3.2.R or VNees Part 1. It is possible to verify the current version of a CEP at any time as well as its status, e.g. valid, suspended or withdrawn, by searching in the Certification Database on the EDQM website www.edqm.eu, under section "Certification of Suitability".

[6] CEP holders responsibilities towards their customers (EDQM Public Document PA/PH/CEP (21) 57).
[7] Guidelines of 16.05.2013 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
[8] Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations
[9] COMMISSION IMPLEMENTING REGULATION (EU) 2021/17 on VNRA
[10] Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "the QP declaration template", EMA/196292/2014
[11] How to read a CEP (EDQM public document PA/PH/CEP (15) 31, see about sites under 4.3.1.)
[12] https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_340_2015_Rev.7_2021_12_clean_-_QA_on_QP_Declaration.pdf

A CTD S section/VNees part 2.C.1. from the manufacturer of the finished product should be elaborated and included in the MA dossier containing the following information:

S.2.1. Manufacturer(s)

Section S.2.1 should be provided in Module 3 of the MAA/MAV and all active substance manufacturing sites actually used should be stated including sites used for quality control/testing of the active substance. The MAH should be aware of which steps of the manufacturing process are performed at which sites, even if not mentioned on the CEP[13] [14] [15].

S.3.2. Impurities and S.4.5. Justification of specification

MAH/applicants and finished product manufacturers should liaise with CEP holders and conduct their own due diligence to ensure they have access to relevant information on actual and potential impurities to be able to set an appropriate specification for active substances in MAAs or MAVs. This includes organic impurities (both process related and degradation products), mutagenic impurities (irrespective of the ICH M7[16] [17] control option accepted during CEP assessment), solvents and elemental impurities, whether or not these are specified on the CEP. The MAH/applicant may need to generate and submit their own information on impurities. During CEP assessment, EDQM reviews limits for impurities not specified in the Ph. Eur. monograph based on the known routes of administration and maximum daily dose (MDD) of already approved medicinal products in which the active substance is used. MAH/applicants referring to a CEP should determine whether the specified impurity limits and control strategy are appropriate for their product, in the case where different indications, posology (e.g. higher MDD, longer duration of treatment) or routes of administration are applied for. This includes mutagenic impurities that may not be specified on the CEP due to the applied and accepted control options during CEP assessment.

In view of potential formation of N-nitrosamine impurities in finished products and to allow the MAH/applicants to perform a risk assessment, information on any impurity containing vulnerable amines such as secondary or tertiary amines that may trigger formation of nitrosamine impurities should be available. The MAH/ applicants should request this information from CEP holders irrespective of the controls applied and even if these impurities in the active substance are present below ICH Q3A/ VICH GL10 identification threshold.

S.4.1. Specification (MAH/applicant/finished product manufacturer* active substance specification)

- The MAH/ applicant/finished product manufacturer's specification for control of the active substance should include all relevant test attributes of the respective Ph. Eur. monograph and all additional test parameters mentioned on the CEP. Since the CEP may not necessarily address all relevant parameters, some finished product specific attributes of the active substance might need to be considered and included in the MAH/applicant/finished product manufacturer's active substance specification in order to ensure that the active substance is of suitable quality for use in a given specific medicinal product (e.g. particle size, polymorphic form, microbial quality, bacterial endotoxins, elemental impurities, …). The active substance specification should clearly indicate

[13] NTA, Volume 2B, Module 1.2. Application form. https://esubmission.ema.europa.eu/eaf/index.html
[14] Module 1: Administrative information Application Form, User guide for the electronic application form for a Marketing Authorisation, CMDh/332/2017, Rev 4, September 2023.
[15] User guide for the electronic Application Form for a Marketing Authorisation and for specific Variations requiring assessment (Veterinary), Version 5.0, April 2023
[16] ICH M7, assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk and ICH M7 Q&A
[17] Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products, EMA/CVMP/SWP/377245/2016
*If the MAH/applicant is different from the finished product manufacturer

which parameters/acceptance criteria/analytical methods are included from the Ph. Eur. monograph, CEP and additional specific attributes.

- Since the CEP reflects the controls for a particular route of synthesis, there may be differences in specification of the active substance from different suppliers/ different CEPs for a given finished product.

If there is more than one supplier of active substance, the MAH/applicant/finished product manufacturer should adopt one single compiled specification for the active substance that takes into account the different impurity profiles of each supplier/source. Test requirements designated to a specific supplier (e.g. residual solvents) should be clearly indicated as such in the specification.

S.4.2. Analytical procedures and S.4.3. Validation of analytical procedures

Analytical procedures used by the MAH/applicant/finished product manufacturer should be described in the MA dossier. If these are the ones of the corresponding Ph. Eur. monograph, a declaration of this will suffice. In addition, the following is expected:

Same analytical methods as used by the CEP holder

In cases where the MAH/applicant/finished product manufacturer uses the same analytical methods as those annexed to the CEP, then the methods should be referenced in the MA dossier and validation data is not required.

Where the methods of the CEP dossier are not annexed to the CEP (i.e. the alternative method of the CEP dossier has been considered equivalent to that of the Ph. Eur. monograph of the active substance by EDQM), they should be described in the MA dossier together with a declaration that the method is the same as assessed and approved by EDQM and validation data is not required.

In-house analytical methods (not used by the CEP holder)

In case where the MAH/applicant/finished product manufacturer uses their own in-house analytical methods, description and validation data should be submitted in the MAA/MAV dossier supporting the suitability of the methods.

Where the MAH/applicant/finished product manufacturer applies additional specification parameters to address finished product specific attributes (e.g. particle size etc.), the corresponding analytical method description and validation data are to be included in the MAA or MAV dossier.

S.4.4. Batch analyses

Sufficient number of batches should be tested by the finished product manufacturer for qualification of the active substance source[18]. Batch results from active substance lots analysed by the finished product manufacturer should be provided demonstrating compliance with the Ph. Eur. monograph, the CEP requirements and any additional tests on critical quality attributes in the MAH/applicant/finished product manufacturer' active substance specification.

S.4.5. Justification of specification

Justification of the MAH/applicant/finished product manufacturer's active substance specification is expected to be provided in section S.4.5 or VNees Part 2.C.1, in particular for those quality attributes established in relation to the finished product. Regarding justification of the control strategy for impurities, see relevant section S.3.2./S.4.5 above.

[18] GMP Part I, chapter 5 – Production/starting materials

S.5. Reference standards and materials

Information should be included on the reference standards of the active substance and impurities used in analytical procedures applied by the finished product manufacturer/MAH/applicant to control the active substance.

S.6. Container closure system

CEPs issued before 1st September 2011 may not include the information on the container closure system of the active substance. In case of absence of this information on the CEP, related data are to be presented in CTD module 3, section S.6. or VNees Part 2.C.3. of the MA dossier. This includes description of the immediate container closure system, including the identity of materials of construction and if appropriate a brief description of any non-functional secondary packaging components. Furthermore, appropriate specifications of the packaging materials and a declaration of compliance with current European food regulations/Ph. Eur. requirements for the packaging material in direct contact with the active substance should be presented.

S.7. Stability

Where no retest period is mentioned on the CEP, stability data may be separately included in the MA dossier for assessment by the Competent Authority to support a retest period.

If the MAH/applicant chooses to apply for a retest period (where no retest is mentioned on the CEP), the stability data provided should reflect the manufacturing process, packaging material (including any use of nitrogen or desiccant) and quality of the active substance described in the relevant CEP.

If the MAH/applicant chooses to test the active substance against the approved specification immediately prior to use in finished product manufacturing, a statement to this effect should be included in the dossier under section S.7. of CTD module 3 or VNees Part 2.F.1 of the MA dossier.

General for all sections

In each individual CTD S. section/VNees part 2.C.1 from the MAH/applicant, where the MAH/applicant does not add any additional information because the information is the same as that present on the CEP, this should be clearly stated and reference should be made to the CEP number and the revision no. of the CEP.

3.3. Specific situations

Some material attributes of the active substance essential to the quality of the finished product may not be listed in the Ph. Eur. monograph or assessed during the Certification procedure. Information relating to these attributes needs to be submitted in module 3 of the MAH/MAV. The data submitted might also depend on the final use of the active substance. Without being exhaustive, a number of examples are given in this section.

What information is to be provided when an intermediate in the synthesis of the active substance is itself an active substance with a monograph in the European Pharmacopoeia (Ph. Eur.) and covered by a valid CEP?

In this case, manufacturer(s) involved in the manufacturing process of the intermediate (as mentioned in the CEP) should be listed in module 3.2.S.2.1. Consequently, these manufacturers should be stated on QP declaration, see also section 4.2.4. of the Guideline on the chemistry of active substances (EMA/454576/2016). In this situation, the manufacturing process, process controls and control of materials from the starting material to the intermediate and corresponding sections are deemed

covered by the CEP. Information on the intermediate (see above S.3.2. and S.4.5.) including the most recent version of the CEP should be presented in section 3.2.S.2.4 of module 3 of the MAA/MAV dossier. In case an ASMF is referred to in the MAA/MAV, the corresponding CEP should be provided in the applicant's part of the ASMF.

What additional information is to be provided in S.3.1. of dossier on physico-chemical characteristics such as polymorphism, particle size, etc when a CEP is referred to?

When a particular grade is not mentioned on the CEP, for example the exact polymorphic form or a specific particle size, micronised or non-micronised grade, the related data (e.g. elucidation of the polymorphic form, or determination of the particle size) should be included in the MAA /MAV dossier where relevant.

In the situation where a subtitle is mentioned on the CEP, the MAH/applicant should justify that the specified grade and applied control is suitable for the intended medicinal product formulation.

Which data to present when a micronisation step is performed but no grade is added as subtitle to the CEP?

When "micronised" is not added as a subtitle on the CEP, details of the micronisation step should be described in the MAA/MAV dossier. The name and address of the micronisation site(s) should be provided (3.2.S.2. or equivalent in VNees format, as described in Q&A 3.1. above). In this case, batch analyses (S.4.4.) and stability data on the micronised material (S.7) according to the stability protocol should be included in the MAA/MAV dossier and the retest period should be set based on the stability of the micronised active substance unless otherwise justified.

The same principles apply to other deliberate particle size reduction steps not covered by the term "micronisation."

If a CEP is referred to a sterile substance, is there any additional data to be submitted in MAA or MAV?

Sterilisation and aseptic processing of active substances are considered to be the first steps of the manufacture of the finished product. In case of sterile substances, the MA dossier should include full information on the sterilisation process and aseptic processing as well as results of any tests applied and validation data of the sterilisation process, even when the CEP states the substance is sterile. More information is found in section 4.2.1 of EU guideline on the sterilisation of the medicinal product, active substance, excipient and primary container[19] and the relevant Q&A[20].

Should additional information on microbial quality be included in the MAA/MAV dossier?

If the Ph. Eur. individual monograph does not make any reference to microbial quality or bacterial endotoxins, required data should be provided in the Module 3.2.S.4 where relevant to the finished product.

Where use of material of human or animal origin is mentioned on the CEP, are additional data needed to demonstrate that viral safety aspects are addressed?

Even if it is stated on the CEP that risk of viral contamination has been considered during CEP assessment, the MAH/applicant should always verify that viral safety aspect of the substance is

[19] Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container, EMA/CHMP/CVMP/QWP/850374/2015

[20] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-1#active-substance---good-manufacturing-practice-compliance-for-sterilisation-of-an-active-substance-section

appropriately addressed for the intended use of the medicinal product and relevant data should be provided in the MAA/MAV dossier. The route of administration or destination animal species (for veterinary medicines) should be considered.

What information should be submitted in relation to the production section of the Ph. Eur. monograph?

In case it is mentioned on the CEP that the statements in the Production Section of the Ph. Eur. monograph have to be addressed in the marketing authorisation dossier, the relevant data have to be included in the MAA/MAV dossier11. The MAH/applicant should liaise with the CEP holder to access the necessary data.

What if the CEP states that residual solvents are controlled according to ICH Q3C option 2?

If the residual solvents have been accepted and controlled according to option 2, this should be considered by the MAH/applicant i.e. further calculation of residual solvents limits may be required in the context of final use in the medicinal product11.

What are the MAH/applicant responsibilities regarding the quality of water used in the manufacturing of the substance covered by the CEP?

Irrespective of the information on the CEP, the manufacturer of medicinal product(s) should verify that the quality of water used in the manufacture of the active substance is appropriate for the intended use of the substance in the medicinal product in particular regarding parenteral formulations and/or apply a suitable control strategy. See 'Guideline on the quality of water for pharmaceutical use'21.

What is to be required as additional data when a CEP covers an API mix?

In case a CEP covers an API mix, description of manufacturing process for preparation of the API mix, stability data and packaging of the API mix (if not stated on the CEP) is to be provided in relevant sections of the MA dossier. See 'Quality Working Party questions and answers on API mix'22. In case such a CEP is provided in a MAV as the new source of the active substance, it should be demonstrated that there is no impact on the currently registered composition of the finished product.

What information should be additionally submitted along with TSE CEPs23**?**

When a TSE CEP is submitted, it should be included in the Regional part of the CTD module 3 (3.2.R) or VNess Part 1.

The MAH/applicant should ensure that the material with the TSE risk is adequate and fit for purpose when this material is used in the manufacture of a medicinal product for veterinary or human use. The final decision on the use of material with TSE risk remains with the Competent Authorities. The acceptability of a particular medicinal product containing such materials shall take into account the following factors: route of administration of the medicinal product, quantity of animal material used in the medicinal product; maximum therapeutic dosage (daily dose and duration of treatment), intended use of the medicinal product and its clinical benefit and presence of a species barrier.

A TSE CEP does not cover viral safety.

MAH/applicants are reminded that in the particular case of gelatine obtained from bones for use in parenteral products, gelatin should be sourced from OIE categories A and B countries.

[21] Guideline on the quality of water for pharmaceutical use, EMA/CHMP/CVMP/QWP/496873/2018
[22] Quality Working Party questions and answers on API mix, EMA/CHMP/CVMP/QWP/152772/2016
[23] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (2011/C 73/01)

What additional aspects should be considered in the MA dossier for Heparins and derivatives?

Heparins and derivatives have been classified as biological products. Therefore, CEPs covering heparins and derivatives cannot substitute the full documentation to be provided in the MAA or MAV dossier of new medicinal products or in a variation. For already approved medicinal products where old CEPs have been accepted, and that have not been withdrawn by EDQM, once the dossier is updated, full documentation according to Module 3 is expected[24] [25].

What additional aspects should be considered in the registration/MAA/MAV dossier for (traditional) herbal medicinal products?

Ph. Eur. monographs for herbal preparations (e.g. extracts or essential oils) cover in many cases different herbal preparations (family monographs) e.g. in terms of different extraction solvents, (e.g. Peppermint leaf dry extract with ethanol or water as extraction solvent).

A single CEP can therefore only cover one specific herbal preparation or herbal drug at a time. The specific herbal preparation to which the CEP refers to, is indicated on the CEP (incl. extraction solvent, DER and excipients).

As limits for herbal relevant contaminants (e.g. pyrrolizidine alkaloids (PA), polycyclic aromatic hydrocarbons (PAH) and elemental impurities) and potentially toxic constituents (e.g. pulegone, menthofuran, estragole) are not mentioned on the CEP, the registration/MA applicant/holder should liaise with the active substance manufacturer. An evaluation of the (potential) content of such impurities in the medicinal product is awaited in the registration/MAA/MAV dossier, along with relevant controls to be implemented, where appropriate.

If limits are applied to the herbal preparation by the CEP holder, the registration/MA applicant/holder should relate these limits with the requirements for the applied herbal medicinal product (e.g. posology, intended age group), in order not to exceed the acceptable daily intake. In the absence of adequate testing by the CEP holder, the registration/MA applicant/holder would have to establish justified limits together with validated analytical procedures.

In case the herbal preparation contains excipient(s), names and quantities of the excipient(s) are listed on the CEP. In order to provide information for the registration/MAA/MAV dossier (composition scheme), the quality of each excipient (e.g. Ph. Eur./USP/in-house) should also be specified by the registration/MA applicant/holder.

Herbal substances/herbal preparations are essentially defined by their production process and their specification. Therefore, in case the herbal medicinal product contains an active substance (e.g. a herbal extract) manufactured by more than one active substance manufacturer, information on each manufacturing process of the active substance should be provided in the registration/MAA/MAV dossier, to allow for comparison.

[24] EMA/CHMP/BWP/429241/2013, section 4.1
[25] https://faq.edqm.eu/pages/viewpage.action?pageId=1377022

4. Changes to the CEP status

4.1. What should be considered in case of CEP revisions?

When a CEP has been revised, a new version is issued which supersedes the previous certificate. The CEP holder is responsible for promptly communicating this to the MA holder providing a signed copy of the latest CEP, highlighting any changes. MA holders should be informed by CEP holders of all changes to the CEP and the API covered by it regardless of whether it leads to a revision of the CEP to evaluate the impact and, if needed, to update the MA information6. As part of any technical agreement in place between the respective stakeholders, it is important that the CEP holder provides an explanation and clarification to the MAH and consequently the medicinal product manufacturer why a revised CEP has been issued e.g. renewal, change of manufacturer, significant change to synthesis, change of specifications etc.

Any MA holder having received a copy of a revised CEP should immediately consider the implications of such changes and as appropriate update any impacted sections of its MA dossier via a MAV application submitted to the relevant competent authorities in line with the established Variation procedures described for human and veterinary medicinal products7, 8, 9. Changes related to quality and/or safety issues should be promptly implemented and corresponding variations submitted. Regarding those changes that can be implemented prior to notification (Type IA for human medicines26 and VNRA for veterinary medicines), the date of implementation that should be specified, is considered to be when the changes are implemented in the relevant pharmaceutical quality systems.

4.1.1 Is it possible to use active substance batches covered by a superseded CEP?

- Batches of active substance manufactured and supplied to the MAH in accordance with a superseded version of the CEP, may still be used for manufacture of the finished product provided there are no quality, GMP and/or safety concerns that have led to the revision of the CEP. In addition, these batches should be:
    - still compliant with the Ph. Eur. Monograph in force at the point of use,
    - tested in compliance with the new specifications of the revised CEP.

An example can be a new specification for nitrosamines on the revised CEP in line with the official acceptable intake (AI) in EU and batches that are tested compliant herewith. Use of AS batches covered by a superseded version of a CEP should be documented in the PQS of medicinal product manufacturer and carried out under the responsibility of the qualified person.

In case the tested batches are not compliant with the new specifications on the CEP, the usual quality defect notification to the National Competent Authority and/or EMA should be used.

- If a CEP is revised as a consequence of a change in the supply chain (i.e. deletion of sites involved in the manufacturing process of the API), unrelated to GMP/quality issues then the material manufactured under the superseded CEP can be considered suitable for use.
- If the change in manufacturing site (deletion) is linked to a GMP issue or quality concerns at the specific site, then the MA holder/manufacturer of FP should assess the impact of the GMP and/or quality issue on batches of medicinal product to be manufactured and/or those manufactured but unreleased or already on the market (potential recalls). Notification should be sent to the Supervisory Authority and NCA using the relevant national procedure for quality defects. In

[26] European Medicines Agency post-authorisation procedural advice for users of the centralised procedure, EMEA-H-19984/03 Rev. 101, Q/A 7.2.4. How should I submit a revised CEP (B.III.1a.2.)

addition, for centrally authorised products, inform the EMA through the EMA quality defect procedure. 27 28

4.2. What should be considered in case of CEP suspensions or withdrawals?

All MA Holders should be immediately notified by CEP holders regarding the changed status of a CEP suspended or withdrawn regardless of the reason. In case the suspension or withdrawal is related to GMP and/or quality issues/ critical failures to the CEP procedure29, the MA holder/manufacturer of FP should assess the impact of the GMP and/or quality issue on batches of medicinal product to be manufactured and/or those already on the market (potential recalls). They should immediately notify their Supervisory Authority and NCA using the relevant national procedure for quality defects. In addition, for centrally authorised products, they should inform the EMA through the EMA quality defect procedure[27] [28].

A CEP suspension applies to all versions of the CEP, as identified by the root number e.g. CEP 2014-XXX (year/chronological number). This situation should remain, until the CEP is either restored, as evidenced by the issue of a newly revised CEP, or withdrawn. In case of revised CEP, a related MAV may need to be submitted.

A CEP withdrawal may also happen for commercial reasons. In any case, the relevant sections of the MA dossier should be updated via a MAV application submitted to the relevant Competent Authorities to reflect the change of status. Any reference to the CEP should be deleted and any consequential amendments to the dossier made.

[27] Compilation of Union procedures on Inspections and Exchange of information, EMA/INS/GMP/84127/2023
[28] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/compliance/quality-defects-recalls#reporting-obligations-section
[29] Suspension or withdrawal of a Certificate of Suitability, Closure of an application, PA/PH/CEP (08) 17, R4