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Certification of suitability to Monographs of the European Pharmacopoeia

CERTIFICATION POLICY DOCUMENT
Content of the dossier for CEP applications for chemical purity and microbiological quality of substances for pharmaceutical use

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CONTENT OF THE DOSSIER FOR CEP APPLICATIONS FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY OF SUBSTANCES FOR PHARMACEUTICAL USE

This document is intended for applicants as a guide for compiling a dossier in order to obtain a Certificate of Suitability (CEP) for chemical purity and microbiological quality.

A new CEP application should contain three modules (Modules 1 – 3).

In this policy document references to guidelines are included to assist applicants. It remains the applicant's responsibility to ensure that all applicable requirements and recommendations, as revised or maintained, are respected. The guidelines referenced in each section provide useful information on the content expected in that section of the dossier. However, this list should not be regarded as comprehensive.

This policy document applies to all substances described in the European Pharmacopoeia and that are within the scope of the Certification Procedure, for assessment of their quality. It mainly applies to active substances but also to excipients described in Ph. Eur. monographs. In case of excipients not all requirements necessarily apply. Included are substances where the manufacturing process is developed on the basis of a traditional approach, an enhanced approach or a combination of both. In situations where elements of Quality by Design have been utilised and design spaces have been claimed, the information in sections 3.2.S.2.2-2.6 should be prepared and organized according to ICH Q11 and ICH Q8, ICH Q9 and ICH Q10, as well as all related EMA/ICH questions and answers documents which give additional guidance as needed.

A CEP application is generally not accepted if the 'crude' substance which is already of European Pharmacopoeia quality is sourced from another Company and the substance undergoes only purification steps.

Module 1

Module 1 should contain a cover letter, a completed application form including relevant declarations and information on the expert (i.e. CV).

The application form "Request for new Certificate of Suitability" with relevant declarations (in annexes) to be completed can be downloaded from the EDQM website (https://www.edqm.eu). When completing the application form, attention should be paid to the following points:

- A subtitle to the CEP should be proposed in box 1.3, only if needed. A subtitle is meant to specify a grade of the substance or to differentiate CEP applications for the same substance from the same holder.

- Commercialisation history of the substance. Applicants should summarise the commercialisation and approval history of medicinal products that contain the substance subject of the CEP application by filling in tables 3.1 and 3.2 in the application form. This information is taken into account during evaluation and if relevant, it would facilitate and accelerate the granting of the CEP.

Declarations:

The application form provides details and a template for each declaration to be submitted.

Each manufacturer involved in manufacturing operations from the introduction of starting material(s) to the final substance, including facilities involved in physical treatments such as micronisation, sterilisation, etc (if applicable) should be listed and appropriate declarations should be submitted.

The following declarations should be provided:

A) For each manufacturing site (both intermediate and final substance manufacturers):

- A declaration signed by the relevant manufacturer that manufacturing operations are conducted in accordance with the presented dossier and that GMP which complies with the relevant parts or Annexes of *EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines* is applied for each manufacturing step from the introduction of the starting materials. If available, a copy of GMP certificates should be provided.
  The EudraLex - Volume 4 - GMP guidelines Part II is applicable to the manufacture of an active substance (API) till the point immediately prior to the sterilisation of the API. If the substance is sterile, sterilisation and aseptic processing should be performed according to EudraLex - Volume 4 - GMP guidelines Annex I.
  For excipients, other approaches to GMP could be acceptable, if adequately justified, refer to *EudraLex - Volume 4 – Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use*.

- When the final substance manufacturer does not belong to the proposed CEP holder, a declaration from the final substance manufacturer committing to keep the proposed holder informed of any changes to the documentation.

- A declaration signed by the relevant manufacturer on willingness to be inspected, before and/or after being granted a certificate of suitability.

B) For the holder:

- When the proposed holder is not the manufacturer of the final substance covered by the CEP application (i.e. does not belong to the same group), a declaration that the holder is willing to be inspected, before and/or after being granted a certificate of suitability.

- A declaration on the use/non-use of material of animal or human origin during manufacture. If material of animal origin which may be susceptible to TSE contamination is used, compliance with the Ph. Eur. General Monograph 1483, *Products with risk of transmitting agents of animal spongiform encephalopathies* should be demonstrated as described in the document *Content of the dossier for a substance for TSE risk assessment* (PA/PH/CEP (06) 2). This would lead to a double CEP (chemical and TSE).

- A commitment to provide samples of the final substance and/or its impurities to the EDQM, if requested. Such a commitment would also be acceptable if provided by the final substance manufacturer.

- Holder's commitments. The applicant should declare that they accept the administrative provisions associated with the Certification Procedure and that they accept that the EDQM shares assessment reports for their application with competent authorities. The holder also commits to inform without delay all their customers of any change made to the CEP application as well as any revision (even if not leading to changes on the CEP), suspension or cancellation of their CEPs. Moreover the holder

commits to provide their customers with suitable and sufficient information from the dossier submitted to the EDQM that may not be mentioned on the Certificate of suitability when granted, in order to enable them to fulfil their responsibilities with regard to the quality, safety and efficacy of the medicinal products containing the substance.

Module 2

Quality Overall Summary (QOS) (2.3)

A summary of the content of the dossier should be given in the form of a Quality Overall Summary (QOS) by using the template available on the EDQM website - (see also Eudralex – *Notice to applicants and regulatory guidelines medicinal products for human use, Presentation and content of the dossier, Volume 2B and Notice to applicants and regulatory guidelines for medicinal products for veterinary use, Presentation and content of the dossier, Volume 6B*).

The QOS should report a brief overview of the manufacturing process, a summary of information on starting materials and a well-prepared overview of the overall control strategy, including a discussion on its suitability to assure batch-to-batch consistency in quality of the substance. The impurity profile of the substance should be reported by filling in the tables and by addressing the different points in the template. It is also expected that the QOS discusses the ability of the European Pharmacopoeia monographs to control the quality of the final substance, and in particular the potential in-house impurities, as well as the necessity for alternative or additional methods, if appropriate.

It is the applicant´s responsibility to ensure that information of both Module 2 and 3 are consistent. A well-prepared QOS would facilitate the evaluation of the CEP application and accelerate the granting of the CEP.

Module 3

Module 3 should be structured according to CTD as defined by ICH M4.

The applicant is reminded that compliance should be demonstrated not only to the individual Ph. Eur. monograph the substance refers to, but to all applicable Ph. Eur. monographs. For example the requirements of the Ph. Eur. General Monograph 1468, *Products of Fermentation*, Ph. Eur. General Monograph 2034, *Substances for pharmaceutical use* and Ph. Eur. General Monograph 1483, *Products with risk of transmitting agents of animal spongiform encephalopathies* should be met, when applicable.

General information (3.2.S.1)Nomenclature (3.2.S.1.1):

The European Pharmacopoeia monograph name, the INN, and other chemical name(s) should be stated together with any laboratory code used in the dossier.

General properties (3.2.S.1.3):

A CEP can cover specific physico-chemical characteristics of the substance (e.g. specific polymorphic forms or particle size distributions) or its sterility. These are generally indicated as “grades” and once approved they are mentioned on the CEP by means of a subtitle.

Where more than one grade is produced with respect to physical characteristics, the manufacturer may wish to apply for one certificate covering all grades, or for separate certificates. In any case, the different qualities should comply with the requirements defined in applicable Ph. Eur. monographs. The possibility for one certificate to cover different grades is accepted only when the impurity profile of the substance remains the same whatever the grade and when these different grades do not require different limits and/or methods for control of impurities. For each grade, the specification describing the determination of the physical grade should be given, with the analytical method used, as well as the characterisation of the physical properties. Batch analysis results, in respect of impurity profiles, should be given for all grades and compliance should also be demonstrated during stability studies, if applicable.

If no grade is meant to be claimed, related information should not be included in the dossier. Statements concerning further processing of the final substance to meet customers' requirements should be avoided.

It should be noted that:

- The use of additives (antioxidants etc.) is only allowed if specifically foreseen by the relevant Ph. Eur. individual monograph, unless it is unambiguously demonstrated that the additive is a process-aid subsequently removed by the process. If an additive is used and this is in compliance with the corresponding Ph. Eur. monograph, then a suitable test method should be provided and validated, and any relevant limits for the additive should be included in the specification and should be justified. If a Ph. Eur. monograph is available, then it is expected that the additive complies with its respective monograph. Further information is available in the EMA Questions and Answers document EMA/CHMP/CVMP/QWP/152772/2016 and in the EDQM guideline *API-Mix (or mixtures) and CEPs* (PA/PH/CEP (16) 70).

  When a carrier oil is used in conjunction with an antioxidant this should be made clear by the applicant. The type of carrier oil should be specified (e.g. sunflower oil, soybean oil etc.). The quality of the carrier oil used should be pharmacopeial grade where applicable. In cases where no Ph. Eur monograph exists, the quality should be justified.

- It is possible to apply for a certificate of suitability for a sterile active substance and the conditions to be met can be found in the documents *Certificates of suitability for sterile active substances* (PA/PH/CEP/T (06) 13) and *Clarification on the acceptability of CEP applications for sterile grade material* (PA/PH/CEP (08) 60) Separate CEP applications are needed if both sterile and non-sterile grades are produced.

- With regard to the TSE risk, where a material used for the manufacture of the final substance can be from either an animal or non-animal source and one source has risk of TSE and the other not, the resulting substances cannot be covered by the same CEP but separate CEPs may be applied for.

- Different polymorphs cannot be described as grades on a single CEP. In case the monograph does not foresee the existence of polymorphism, requests for specific polymorphic forms as grades can be accepted provided that the applicant demonstrates that the substance indeed shows polymorphism. Literature or any other evidence should be provided in support.

In the particular case where the Ph. Eur. monograph covers different grades of the substance (e.g. sodium hyaluronate or macrogols), it is possible to cover them with the same CEP application if the quality of the substance is in compliance with the requirements of the monograph, whatever the grade.

"Functionality related characteristics" sections of Ph. Eur. monographs do not constitute mandatory requirements but these characteristics may be relevant for particular uses of the substance for pharmaceutical use. It is therefore possible but optional to cover those characteristics as needed.

Applicants are requested to state in section 3.2.S.1.3 the maximum daily dose (MDD), route of administration and treatment duration considered for the development of their control strategy and specification presented. This information should be based on human medicine European public assessment report (EPAR), summary of product characteristics (SmPCs), or agreed literature such as Martindale. References should be provided.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1):

All sites involved in the manufacture of the substance after the introduction of the starting material(s), including quality control and in process testing sites (contractors included), should be listed in section 3.2.S.2.1 with their name, address and role but also with the SPOR/OMS Organisation (ORG) and Location (LOC) ID.

Only if a grade is claimed, sites in charge of the applicable physico-chemical treatments such as milling, micronisation and sterilisation should be listed.

Description of manufacturing process and Process Controls (3.2.S.2.2):

Where materials described in the Ph. Eur. are introduced into the process typically as intermediates or starting materials and these materials are covered by a CEP, their CEP can be provided in the new CEP application to describe their quality. The EDQM guideline *Use of a CEP to describe a material used in an application for another CEP* (PA/PH/CEP (14) 06) gives details of the information needed at the time of submission of the application.

The following information should be provided with regard to all operations conducted from the introduction of starting materials onwards (manufacturing process of the substance for pharmaceutical use and all outsourced intermediates, if any):

- An outline of the synthetic process or flow diagram, including the structural formula for the starting material(s) and all intermediates (including in-situ non-isolated intermediates, indicated between squared brackets), accompanied by all solvents, reagents, catalysts and process-aids used in the process.

- The description of the manufacturing method should include all the steps of the process, proceeding from the starting materials(s) to any isolated intermediates, and ultimately to the final substance including physical treatments such as micronisation or sterilisation, etc.

- Detailed description (in a narrative form) of each stage of the manufacture, including information on solvents and reagents, catalysts, process aids, operating conditions of reactions, information on intermediates (non-isolated, isolated and purified), quantities of all materials used in the process to produce a batch of the typical commercial size and yields for isolated intermediates should be indicated for each process step. Special emphasis should be given to the final steps, including

purification procedures. The submission in section 3.2.S.2.2 of Master Batch Records should be avoided.

- The maximum batch size (or range) for which the manufacturer has acquired experience with the defined method, and which should correspond to batches referred to in the dossier, should be stated. Where the substance has yet to be produced in commercial quantities (only pilot scale batches manufactured) the certificate may be granted provided scale-up is reported to the EDQM via a revision procedure. For a sterile product, an application for a variable and/or alternative batch size should be justified.

- Different manufacturing sites for the final substance can be described in a single application provided that all manufacturing sites belong to the same group.

- Whatever type of manufacturing process is used, alternatives within the same dossier are only allowed if not substantially different. Even if the quality of late stage key intermediates and final substance from the alternative process are not affected in terms of specification and impurity content but the processes are substantially different, they cannot be accepted in the same application. A separate CEP application covering the same substance with the difference(s) explained in a subtitle may need to be submitted for each alternative process.

- The micronisation operation should be described in the dossier if the CEP covers the micronised quality of the substance. Unit operations such as milling or micronisation including the type of equipment used and the characteristic process parameters should be described. A discussion on the influence of milling or micronisation on the quality of active substance should be provided, supported by data.

- In case of sterile substances, a detailed description of the sterilization steps should be provided.

The control of critical steps and intermediates should be described in 3.2.S.2.4.

The steps where reprocessing is carried out should be identified and justified. Batch data to support this justification should be presented in the dossier. The reprocessing procedure should be clearly described and quality attributes triggering reprocessing if outside the predefined acceptance criteria should be identified.

Re-working (application of steps different from those of the approved process) is normally not acceptable since this implies the use of different solvents, which would lead to a change in the specification, physico-chemical characteristics and/or impurity profile of the substance. Re-working procedures should not be included in the dossier and should be carried out according to ICH Q7.

Recovery (e.g. from mother liquors or filtrates) of reactants, solvents, intermediates or the final substance is considered acceptable provided that validated procedures exist for the recovery and that the recovered materials meet specifications suitable for their intended use. It should be described where materials are recovered from and re-introduced into the process. Justified specifications should be described for recovered material(s). Recovery procedures should be fully described in section 3.2.S.2.2.

Blending of production batches of final substance to obtain a larger size is acceptable provided that each batch is individually tested prior to blending and complies with the specifications of the final substance.

Control of materials (3.2.S.2.3):

All materials used in the manufacture of the substance (starting materials, solvents, reagents, catalysts, process aids, etc.) should be listed identifying where each material is used in the process.

Starting materials

Applicants should propose and justify which substance(s) should be considered as the starting material(s) and this should follow the principles and guidance described in ICH Q11 and the corresponding Questions and Answers, the EMA *Guideline on the chemistry of active substances* (EMA/454576/2016) and the EMA *Guideline on the chemistry of active substances for veterinary medicinal products* (EMA/CVMP/QWP/707366/2017), as needed.

Cell banks are the starting point for manufacture of fermentation products.

Generally, only a flow chart of the syntheses of the proposed starting material(s) should be provided, including solvents, reagents and catalysts used. The impurity profile of starting material should be sufficiently understood and described. Any limitation in understanding the impurity profile of a starting material should be explained and justified along with a discussion on the impact on the impurity profile of the final substance. The specifications should reflect the synthetic strategy adopted and should include acceptance criteria for purity and/or assay, as well as impurities (specified, unspecified and total impurities, residual solvents, reagents including daughter-compounds, elemental impurities and mutagenic impurities), as needed. Acceptance criteria should be justified by information on fate and purge of impurities, supported by data as needed. Descriptions of associated analytical methods or a reference to a pharmacopoeial method should be provided. With regard to the validation of those methods, the principles of the guideline on chemistry of active substances should be followed.

Control and absence of carry-over of potential impurities (unchanged or as downstream derivatives) from the starting material to the final substance (including solvents, reagents) should be discussed and demonstrated as appropriate.

The name and address of the manufacturer(s) of the starting materials(s), not suppliers, should be provided and if more than one manufacturer is declared for the same starting material, batch analysis results on the final substance (or a suitable intermediate) manufactured using each source of declared starting materials should be provided.

If any animal-derived material is used during the manufacture of the starting material (including fermented starting materials), this should be declared, and if applicable, the risk of transmitting agents of animal spongiform encephalopathies should be addressed. For semi-synthetic drug substances (where starting material is obtained from fermentation or by extraction from botanical material), the impurity profile of the fermented or extracted starting material should be sufficiently understood and appropriately discussed. Regarding fermented starting materials in addition to typical impurity discussion (as mentioned above), the possibility of specific impurities (e.g. DNA, proteins etc.) from the fermentation process to the final substance should be discussed. Similarly, for starting materials of herbal origin the potential presence of foreign matter, pesticides, fumigants, microbiological contamination, total ash, elemental impurities, mycotoxins (aflatoxins, ochratoxin A, etc.), radioactive contamination, residual solvents, and other relevant impurities should be discussed as far as relevant for the material, and, where applicable, demonstrated absent. The EMA Q&A on *Starting materials of herbal origin* and the Ph. Eur. monograph on *Herbal Drugs* (1433) should be consulted as needed.

Final substances obtained only by purification or salification of a fermented starting material cannot be considered as semi-synthetic substances and should therefore be subject to the same requirements as products of fermentation.

Other materials

Appropriate specifications and information on analytical methods should be provided for all other materials (solvents, reagents, catalysts, processing aids etc.) used in the manufacturing process. It is expected that the specification contains at minimum identification, assay, and control of impurities, unless otherwise justified. The closer to the final substance, the more detailed the impurity control of other materials should be considered. Control of class 1 solvents as potential contaminants in relevant solvents should be taken into consideration, especially for solvents used in final purification steps.

Recycled materials should comply with justified specifications, before being reintroduced into the process. The impact of using these recycled materials on the final impurity profile should be addressed, as needed.

Peptone is considered to be a critical raw material, whose origin (animal or vegetable) and source (supplier name and address) is expected to be specified in the dossier. According to the origin of peptone used, the expectations below are meant to be taken into account:

- If material of fish origin, peptones included, are used, refer to the expectations in the FAQ "What should we do if we manufacture an active substance using a fermentation process that uses materials of fish origin, including peptones?" available on the EDQM website (https://faq.edqm.eu/pages/viewpage.action?pageId=37814281).

- If peptones are not of fish origin, you should refer to the expectations in the FAQ "What should we do if we manufacture an active substance using a fermentation process that uses peptones that are not of fish origin?" available on the EDQM website (https://faq.edqm.eu/pages/viewpage.action?pageId=37814284).

- If material of fish origin is used but the active substance is manufactured without using a fermentation process, you should refer to the expectations in the FAQ "What should we do if we manufacture an active substance that does not use a fermentation process but does use a material of fish origin?" available on the EDQM website (https://faq.edqm.eu/pages/viewpage.action?pageId=37814286).

Limits could be based on the acceptable intake for histamine of 2.1 µg/day.

The quality of the water used within the manufacturing process should be in line with the EMA *Guideline on the quality of water for pharmaceutical use* (EMA/CHMP/CVMP/QWP/496873/2018) which specifies the acceptable grades of water used during manufacture of active substances. The quality of water used should be defined referring to the Ph. Eur. (e.g. purified water, water for injections, etc).

Controls of critical steps and intermediates (3.2.S.2.4);

Tests and acceptance criteria performed at critical steps identified in 3.2.S.2.2 of the manufacturing process should be described, and justified based on relevant experimental data, in line with EMA *Guideline on the chemistry of active substances* (EMA/454576/2016). Analytical procedures should be described.

A suitable and detailed specification (including at least tests for identification, purity and/or assay, related substances, residual solvents, reagents, elemental and mutagenic impurities, unless otherwise justified) is expected for isolated intermediates, along with analytical methods descriptions. With regard to the validation of those methods, the principles of the guideline on chemistry of active substances should be followed. The impurity profile of isolated intermediates should be understood and major and recurrent impurities should be identified. Specifications should be justified by means of information on fate and data on carry-over of impurities introduced with isolated intermediates to the final substance.

Where there is more than one manufacturer declared in the dossier for the same intermediate (provided that the syntheses are not significantly different), batch analysis results of the final substance (or subsequent intermediate) manufactured using all declared sources of intermediates should be provided.

Process validation and/or evaluation (3.2.S.2.5)

Process validation and/or evaluation studies should be provided in applications for sterile substances. The full description of the sterilisation process together with full validation data (protocols and reports) should be presented in the dossier. The EU guideline on sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) should be considered.

Production section in the Ph. Eur. monograph:

When the monograph indicates specific requirements for the manufacturing process in the production section of the monograph, compliance to this aspect should be demonstrated when reference to a specific test(s) is given. If the requirement is chemical in nature (e.g. control of enantiomeric purity or mutagenic impurities), compliance is assessed during the evaluation procedure and the data in support should be presented in the dossier. Compliance to the production sections in Ph. Eur. monographs is assessed in the context of the Certification Procedure in the vast majority of cases. If not assessed this requirement is addressed by national authorities during evaluation of marketing authorisation application.

Where substances are manufactured by an enhanced approach (Quality by design including continuous manufacturing or process analytical technology concepts derived from ICH Q8 - Q11) then appropriate data should be presented under relevant sections. Preferably, the corresponding development data should be provided in section 3.2.S.2.6.

It is recommended that any data from process validation activities which is considered relevant to support the ability of the process to purge impurities is included in the dossier.

Characterisation (3.2.S.3)

Elucidation of Structure and other Characteristics (3.2.S.3.1)

As stated in the Ph. Eur. General Notices (10000), in the EU guideline on *summary of requirements for active substances in the quality part of the dossier* (CHMP/QWP/297/97, EMA/CVMP/1069/02) and in the EMA guideline on chemistry of active substances (EMA/454576/2016, EMA/CVMP/QWP/707366/2017), if a suitable identification test (e.g. IR) is described in a Ph. Eur. monograph with an appropriate reference standard, other structural evidences may not be needed. If a suitable reference standard is not available, then appropriate characterisation should be submitted.

If specific grades are claimed on polymorphism or particle size distribution, relevant data should be presented. If a grade on a specific polymorphic form is requested, it should be evident from presented data

which polymorphic form is produced and that the same form is consistently produced by the applied manufacturing process. Stability of polymorphic form over the proposed re-test period should also be demonstrated, in case a re-test period is requested.

Impurities (3.2.S.3.2)

It is expected that a detailed impurity discussion is provided. This does not only concern related substances, but all potential impurities resulting from the manufacturing process (i.e. reagents, solvents, catalysts, chelating agents, by-products and other raw materials). If the monograph does not contain a suitable test to control these potential impurities a discussion and demonstration of absence or establishing adequate controls are expected. Specific attention should be directed to materials used in the last steps of the manufacturing process. A description of the corresponding analytical methods, including minimum validation data (i.e. specificity and sensitivity) should be provided. LOD and LOQ values should be reported in per cent or ppm with regard to the final substance, where possible.

In case of optically active substances a specific discussion on their stereo-chemical purity is expected.

Related substances

The requirements of the related substances section of the Ph. Eur. General Monograph 2034*, Substances for Pharmaceutical Use* should be met. It should be demonstrated that all applied methods are suitable to control impurities at the applicable levels set by the general monograph. Furthermore, the provisions of the Ph. Eur. general chapter 5.10 *Control of impurities in substances for pharmaceutical use* are to be taken into consideration.

A discussion on related substances of a substance for pharmaceutical use which is based only on impurities listed in the transparency statement of the monograph is rarely considered as sufficient. The discussion should be based on the actual process-related and degradation impurities resulting from the adopted manufacturing process described in the dossier. The impurities that are controlled should be presented together with details of the analytical methods used, and a list of the related substances found in the substance. The related substances found in batches of the final substance should be compared with the related substances listed in the transparency statement of the monograph (where one exists) together with their typical levels and the proposed limits.

The suitability of the method(s) of the monograph to control the quality of the substance must be discussed and demonstrated. In particular, where additional impurities (i.e. those not listed in the transparency statement of the monograph) are detected above the relevant reporting threshold or the disregard limit of the monograph, the ability of the methods of the monograph to control these impurities must be demonstrated. Where applicable, retention times, correction factors and limits of detection/quantification should be provided. If the methods of the monograph are not suitable to control the additional impurities, suitably validated additional test(s) should be proposed and the method validation should be provided. Evidence should be given of the absence of impurities not routinely tested for in the final substance or its intermediates.

Example of chromatograms for production batches of the substance suitably zoomed and annotated and with peak area results should be supplied.

Where additional related substances are present (those not already mentioned in the monograph), the corresponding limits should be established according to the related substances section in the Ph. Eur.

General Monograph 2034*, Substances for Pharmaceutical Use*. Impurities detected above the relevant identification threshold should be identified and impurities present above the relevant qualification threshold should be qualified. Where necessary, toxicological data should be supplied in support. Alternatively, and where appropriate, it may be demonstrated by other means that the impurity profile of the substance is comparable to that of products already on the European market.

For substances out of scope of the Ph. Eur. General Monograph 2034*, Substances for Pharmaceutical Use* containing impurities that cannot be controlled by the monograph's criteria for related substances, suitable limits should be proposed and where necessary toxicological data should be supplied. Particular emphasis is directed to antibiotics and the provisions laid out in the *Guideline on setting specifications for related impurities in antibiotics* (EMA/CHMP/CVMP/ QWP/199250/2009). For substances out of scope of both General Monograph 2034 and the guideline on setting specifications for impurities in antibiotics, the general principles as stated in these documents still apply. The applicant should define justified thresholds and discuss the impurity profile of their substance accordingly.

Mutagenic impurities

In line with ICH M7 guideline, a specific discussion on potential mutagenic impurities should be provided as part of the overall discussion on impurities. It is expected that potential mutagenic impurities arising from the synthesis of the final substance and its starting material(s) as well as degradation products are listed and classified (class 1 to class 5) in the dossier as per ICH M7. Toxicological data in support of this classification should be provided, as needed. If a mutagenic impurity is liable to be present in the substance a control strategy in line with ICH M7 should be proposed. Only demonstrating absence of concerned impurities may not be sufficient to support compliance to ICH M7. In addition, the applicant is requested to provide in section 3.2.S.3.2 a comprehensive risk assessment to address possible formation of N-nitrosamine impurities in substances for human use. If a risk is identified, a suitable control strategy should be introduced. The risk evaluation should not only address risks related to the manufacturing process, but also those deriving from the introduction of materials used in the manufacturing process and other potential sources of contamination (e.g. starting materials, reagents, solvents, recovery of materials, equipment, degradation). Any risk concerning formation and carry-over of N-nitrosamines should be addressed taking into account the EMA Q&A document EMA/409815/2020. In general, when discussing possible degradation products, reference to data from real time stability studies or from stress testing or reference to the literature may be helpful. However, results from formal stability studies are not a requirement when there is no request to mention a re-test period on the certificate.

In regard the substances for veterinary use only, the discussion on mutagenic impurities should be given in a similar way following the recommendations established in the *Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products* (EMA/CVMP/SWP/377245/2016).

Other impurities

If the monograph does not provide a suitable test for residues of toxic reagents, the presence of such residues should also be discussed and where applicable, a suitable limit should be proposed along with the description of corresponding sufficiently validated test method.

Residual solvents

The Ph. Eur. general chapter 5.4 *Residual Solvents* is applicable. In addition, the Annex I: specifications for class 1 and class 2 residual solvents in active substances (CPMP/QWP/450/03, EMEA/CVMP/511/03) should be taken into consideration when setting specifications.

If class 2 solvents are used in a step of the manufacturing process prior to the final purification, the absence of such solvents in the final substance should be demonstrated to justify omission of any testing. Otherwise a suitable test should be introduced. In general, the solvents to be controlled in the final substance specification are all the solvents used in the last purification steps and any class 2 and class 3 solvents found above 10% of their respective ICH limit (as described in *Annex I: Specifications for class 1 and class 2 residual solvents in active substances*).

As indicated in the Ph. Eur. general chapter 5.4, class 1 solvents should not be employed in the manufacture of substances for pharmaceutical use, unless their unavoidability is scientifically demonstrated and a benefit/risk justification is provided.

Any limit higher than the (V)ICH option 1 limit should be set according to an option 2 calculation, i.e. based on the maximum daily dose (for class 2 solvents only) and should be justified by batch data reflecting the actual process capability. Low toxicity solvents (Class 3) can be limited by a test for loss on drying with a limit of not more than 0.5%, when appropriate. If the limit of the loss on drying test of the monograph is higher than 0.5%, then a specific test for residual solvents should be introduced.

A toxicological justification should be supplied for any proposed limits for solvents that are not listed in the general chapter or listed in table 4 of the general chapter and which need to be introduced in the specification of the final substance.

Elemental impurities

A specific discussion on elemental impurities should be provided. Elemental impurities include, but are not limited to, reagents and catalysts which are intentionally introduced in the manufacturing process. The applicant may choose to provide or not a risk assessment on elemental impurities, as described in ICH Q3D or, for substances for veterinary use only, in RP on risk management requirements for elemental impurities in veterinary medicinal products EMA/CVMP/QWP/153641/2018 and in the EDQM guideline *Implementation of policy on elemental impurities in the Certification Procedure* (PA/PH/CEP (16) 23). The risk assessment should be supplemented with a risk management summary in a tabular format (RMS) intended to be appended to the CEP (see annex of the aforementioned EDQM guideline). This guideline also clarifies what is necessary in case elemental impurities are intentionally introduced in the manufacture of the final substance. The use of the RMS is encouraged.

Control of Drug substance (3.2.S.4)

Specification (3.2.S.4.1)

The specification should be defined in accordance with the applicable current general and specific European Pharmacopoeia monographs. Where the monograph was demonstrated to be not suitable to control the quality of the substance, in particular with respect to the impurities, additional analytical methods should be established. Any additional tests to those of the monograph should be justified.

Specification should reflect the quality claimed. If a grade is claimed, related controls (such as particle size distribution, identification of specific polymorphic forms, etc) should be included in the specification.

Where the monograph includes a production section, the requirements of this section should be met, as applicable. For chemical or analytical production requirements, the applicant should provide a discussion and appropriate methods (including data) to enable evaluation. If the requirement is biological in nature, this is not evaluated by EDQM.

Drug substances that are declared to be sterile must be in compliance with the Ph. Eur. general test 2.6.1 *Sterility*.

The specification for the substance should preferably not include tests implemented to comply with other pharmacopoeias than the Ph. Eur. (e.g. USP). The specification should be presented in tabular format. Parameters (along with the analytical technique used), limits and reference of the method, (e.g. Ph. Eur. or in-house), should be clearly reported in the table. In case of in-house impurities controlled in the substance, an unequivocal chemical name of the compound should be used (in-house code may be added if relevant). In addition, the specification of the substance should contain only information corresponding to the quality claimed.

European Pharmacopoeia monograph under revision

If the monograph is in the process of being revised, the draft monograph may be taken into consideration during evaluation. Therefore, the manufacturer may also wish to take it into consideration in the dossier in particular with regard to impurities and their limits. However, application of a revised monograph is not mandatory before the implementation date.

Analytical procedures (3.2.S.4.2)

If test methods other than those described in the Ph. Eur. monograph are used, they must be fully described and validated (see below). Details of the methods of the Ph. Eur. monograph should not be reproduced in section 3.2.S.4.2. This applies also in case chromatographic adjustments are made to the Ph. Eur. method within the scope of Ph. Eur. chapter 2.2.46.

Analytical procedures should be described in such a way that they can be repeated by a competent analyst. The level of details given in the Ph. Eur. monographs can be used as an example.

Monographs describing a TLC method to control related substances are not considered to comply with the requirements of the Ph. Eur. General Monograph 2034, *Substances for Pharmaceutical Use* and general chapter 5.10 *Control of impurities in substances for pharmaceutical use*. Therefore, a quantitative method should be proposed by applicants to control the related substances liable to be present in the substance, in replacement of the compendial one.

Where the monograph has a labelling section and/or functionality-related characters, and where a subtitle is to be included on the CEP, the relevant analytical methods to determine compliance to the specifications should be presented in the dossier and shown to be suitable.

To facilitate the preparation of the certificate, a separate description of any supplementary tests should be presented. Moreover applicants are expected to divide the analytical test procedures for their substance into two distinct subsections and to provide “clean” documents. Details are reported below.

- Subsection 1 - Alternative in house analytical test procedures to those of the Ph. Eur. Monograph. This section should include any in house analytical test procedures, which following validation and cross validation with the method of the Ph. Eur. monograph, have been determined to be equivalent. All analytical test procedures provided in subsection 1 should be fully described.

- Subsection 2 – Additional in house analytical test procedure(s). This section should include any additional in house analytical test procedures that are required to control the quality of the substance. Those additional methods are methods, which are either not detailed in the Ph. Eur. monograph for the substance or which are applied when the Ph. Eur. monograph methods are not suitable to control impurities or which are used to control additional parameters (e.g. particle size distribution). These analytical test procedures should be fully described in this section, and should be appropriately validated. The method description should be legible and the use of scanned documents is to be avoided. Applicants are encouraged to avoid the addition of headers, footers and supportive chromatograms in section 3.2.S.4.2 of their submissions as they would be removed by EDQM during the preparation of the CEP.

Validation of analytical procedures (3.2.S.4.3)

If test methods other than or supplementary to those of the European Pharmacopoeia are used, the analytical validation should be supplied. Where the official method of control of related substances is used, and it is declared that only those related substances listed in the transparency statement of the monograph are present in the final substance, it should be demonstrated that no other impurities are detected. Typical chromatograms should be presented. If the applicant uses an in-house method (alternative method) instead of the relevant Ph. Eur. method for quality control of the final substance, then the method(s) should be adequately validated according to ICH Q2 (VICH GL1 and GL2) recommendations and cross-validated with reference to the monograph's method(s). At the minimum, comparison of data from three batches tested with both methods should be provided to support their equivalence in response. The use of samples with known (spiked) quantities of impurities is recommended in case of very pure substances.

If an additional method (e.g. residual solvents) is exactly in line with the general methods of the European Pharmacopoeia (i.e. General Method 2.4.24 for residual solvents), a full validation is not required. However, the method should be described and applicability to the concerned substance should be demonstrated. For the determination of residual solvents, the method of sample preparation and the used system (A or B) should be specified. Methods from a specific monograph of another Pharmacopoeia of a Ph. Eur. member state do not have to be fully validated (though specificity needs to be demonstrated and level of detection and/or quantification should be determined). If the method of the specific monograph is used to control additional impurities, a minimum validation should be done (specificity and limits of detection and quantification).

If grades are requested, validated methods for determination of specific quality attributes that characterise the grades should be provided, along with appropriate acceptance criteria.

Batch analyses (3.2.S.4.4)

Batch results of full testing of at least three recent consecutive batches should be included and should comply with the acceptance criteria of the monograph and any other additional/relevant test. Results below 1.0 per cent for related substances should be reported with two decimal places, e.g. 0.25 per cent. When different sources of starting materials, different grades, different sites (belonging to the same group) or methods of manufacture or alternatives (which are not substantially different) are described in the dossier, the results of analysis of the batches should be provided for each of them. The batch size, batch number and the date of manufacture/analysis should be indicated. The results of analysis should be reported as actual figures whenever possible, instead of statements such as “conforms”, “complies”, etc.

The batch size should be in accordance with the declared batch size/range as specified in the description of the manufacturing process in section 3.2.S.2.2.

Justification of specification (3.2.S.4.5)

It should be stated if supplementary or improved tests, compared to the monograph, are needed. Any additional limits or deviations should be justified. The possible need for a revision of the European Pharmacopoeia monograph should be discussed.

Omission of tests

Where the monograph mentions a test for a named impurity which is not possible according to the manufacturing process described, the manufacturer may omit the test for this specific impurity in the specification. However, this should be clearly indicated in the dossier. If the proposal of the applicant is accepted, a formal statement on this subject will be reported on the CEP. However, the substance should comply with the monograph, if tested.

Reference standards or materials (3.2.S.5)

When in-house standards/working standards, non-official or official standards other than the appropriate Ph. Eur. CRS are employed, they should be suitably described (in terms of identification, purity, assay, etc.) and their establishment demonstrated. If other standards are used instead of their respective Ph. Eur. CRS, an appropriate comparison to the Ph. Eur. CRS is required (e.g. IR spectra).

Container-closure system (3.2.S.6)

The container-closure system should be described including all its components and the specifications should be supplied. It is expected that an identification test (e.g. IR) is performed on the primary packaging material. Where relevant, conformity to the relevant Ph. Eur. monographs and the EU guideline on *Plastic Primary Packaging Materials* (CPMP/QWP/4359/03 and EMEA/CVMP/205/04), should be demonstrated. It is expected that declarations of compliance to current EU regulations on plastic materials and articles intended to come into contact with food (10/2011 and subsequent amendments) are provided for primary packaging materials.

Depending on nature of the active substance, aspects that may need justification include choice of the primary packaging materials, protection from light and/or moisture, compatibility with the active substance including sorption to material and leaching and/or any safety aspects. Reference to stability data can be additional supportive information to justify suitability of the proposed container closure system. The

information should cover the whole packaging including the primary packaging material (e.g. polyethylene bag) and secondary packaging (e.g. fibre or metal drum).

Stability (3.2.S.7)

As stated in the EU guideline on *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02), for active substances described in an official pharmacopoeial monograph (Ph. Eur. or the pharmacopoeia of an EU Member State) which covers the degradation products, and for which suitable limits have been set but a re-test period is not defined, results from stability studies are not necessarily required, provided that the active substance complies with the pharmacopoeial monograph immediately prior to use in the finished product. For substances for veterinary use only, the EU Regulation 2021/805 states that re-test period and storage conditions for the active substance shall be specified except when the manufacturer of the finished product fully re-tests the active substance immediately before its use in the manufacture of the finished product.

When a re-test period is requested to be mentioned on the certificate (option which is highly encouraged and be made clear on the application form) it should be determined in accordance with applicable (V)ICH guidelines, the EU guideline on *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02 and EMEA/CVMP/846/99) and the Annexes: *Declaration of Storage Conditions: in the product information of Medicinal Products and for Active Substances* (CPMP/QWP/609/96) and *Declaration of Storage Conditions: In the product information of pharmaceutical veterinary medicinal products and for active substances* (EMEA/CVMP/422/99). Results from long term and accelerated stability studies justifying the requested re-test period and in accordance with the guidelines shall be supplied.

If no retest period is requested, stability data may still be provided in the dossier to support discussions on the impurity profile of the substance and justify control strategies.

The information and recommendations given under the heading “Storage” in the Ph. Eur. monograph does not constitute a requirement and are given for information only (see Ph. Eur. General Notices).

Compliance to the stability-indicating quality attributes in the individual Ph.Eur. monograph the substance refers to should be demonstrated during the whole re-test period of the substance. If a specific grade is claimed, the substance with that quality and grade should be included in the stability testing programme and the stability of the corresponding parameter should also be demonstrated over the proposed re-test period as needed.

As an option, CEP holders/applicants are given the possibility to refer to climatic zones, known as zones III and IVA and IVB, in addition to zones I and II. It is up to CEP holders/applicants to decide and state the climatic zone they refer to. The WHO Technical Report Series, No. 1010, 2018 should be used for the definition of storage conditions.

Restrictive storage conditions with respect to temperature may be accepted, provided they correspond to the conditions in which stability data have been obtained.

Different re-test periods and storage conditions can be proposed within one CEP application (e.g. different re-test period depending on the container closure system or climatic zone).Applicants are encouraged to apply for a re-test period even with limited stability data, with the understanding that suitable data to justify the wanted re-test period should be provided during the evaluation procedure.

Post-approval Stability Protocol and Stability Commitment (3.2.S.7.2)

A re-test period may be attributed based on extrapolation proposed by the applicant under the conditions described in the EU guidelines on *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02 and EMEA/CVMP/846/99) and *Evaluation of Stability Data* (CPMP/ICH/420/02 and EMA/CVMP/VICH/858875/2011). In this case, and also when the re-test period has been based on data obtained on pilot batches, the manufacturer will be asked to supply the complementary and/or additional stability data when available.

A post-approval stability protocol and stability commitment should be provided if data for production scale batches covering the full proposed re-test period are not available.

References

List of referenced policy papers and guidelines

Eudralex	*Notice to applicants and regulatory guidelines medicinal products for human use, Presentation and content of the dossier, Volume 2B*
Eudralex	*Notice to applicants and regulatory guidelines for medicinal products for veterinary use, Presentation and content of the dossier, Volume 6B*
Eudralex	*Volume 4 - Good Manufacturing Practice (GMP) guidelines*
Eudralex	*Volume 4 - Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use*

EDQM Guidelines	**Title**
PA/PH/CEP (06) 2	Content of the dossier for substances for TSE risk assessment.
PA/PH/CEP (16) 70	API-mix (or mixtures) and CEPs.
PA/PH/CEP (14) 06	Use of a CEP to describe a material used in an application for another CEP.
PA/PH/CEP/T (06) 13	Certificates of suitability for sterile active substances.
PA/PH/CEP (08) 60	Clarification on the acceptability of CEP applications for sterile grade material.
PA/PH/CEP (16) 23	Implementation of ICH Q3D in the Certification Procedure.
https://faq.edqm.eu/pages/viewpage.action?pageId=37814281	What should we do if we manufacture an active substance using a fermentation process that uses materials of fish origin, including peptones?
https://faq.edqm.eu/pages/viewpage.action?pageId=37814284	What should we do if we manufacture an active substance using a fermentation process that uses peptones that are not of fish origin?
https://faq.edqm.eu/pages/viewpage.action?pageId=37814286	What should we do if we manufacture an active substance that does not use a fermentation process but does use a material of fish origin?

Ph. Eur. general monographs, general chapters and general tests and methods	**Title**
General notices 10000	General notices
General monograph 2034	Substances for Pharmaceutical Use.
General monograph 1483	Products with risk of transmitting agents of animal spongiform encephalopathies.
General monograph 1468	Products of Fermentation.
General chapter 5.10	Control of impurities in substances for pharmaceutical use.
General chapter 5.4	Residual Solvents.
General Test 2.6.1	Sterility
General Method 2.4.24	Identification and control of residual solvents
General monograph 1433	Herbal drugs and herbal drug preparations

General Method 2.2.46	Chromatographic separation techniques

EU/(V)ICH Guideline	**Title**
CPMP/ICH/381/95	ICH Q2 “Validation of analytical procedures: text and methodology”
CVMP/VICH/590/98	VICH GL1 “Guideline on validation of analytical procedures: definition and terminology”
CVMP/VICH/591/98	VICH GL2 “Guideline on validation of analytical procedures: methodology”
CPMP/ICH/2887/99	ICH M4 “The common technical document. (CTD) for the registration of pharmaceuticals for human use - Organisation of CTD”
EMA/CHMP/ICH/425213/2011	ICH Q11 “Development and manufacture of drug substances (chemical entities and biotechnological/ biological entities)”
EMA/CHMP/ICH/167068/04	ICH Q8 “Pharmaceutical development”
EMA/454576/2016	Chemistry of active substances (chemistry of new active substances)
EMA/CVMP/QWP/707366/2017	Chemistry of active substances for veterinary medicinal products
CHMP/QWP/297/97, EMEA/CVMP/1069/02	Summary of requirements for active substances in the quality part of the dossier
EMA/CHMP/ICH/24235/2006	ICH Q9 “Quality risk management”
EMA/CHMP/ICH/214732/2007	ICH Q10 “Pharmaceutical quality system”
Eudralex	Vol. 2B. Notice to applicants and regulatory guidelines medicinal products for human use, Presentation and format of the dossier
EMA/CHMP/CVMP/QWP/199250/2009	Guideline on setting specifications for related impurities in antibiotics
EMA/CHMP/ICH/83812/2013	ICH M7 “Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk”
EMA/CVMP/SWP/377245/2016	Assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products
CPMP/ICH/283/95 CVMP/VICH/502/99	ICH Q3C, VICH GL18 “Impurities: Guideline for Residual Solvents”
CPMP/QWP/450/03 EMEA/CVMP/511/03	Annex 1: Specifications for Class 1 and Class 2 residual solvents in active substances.
EMA/CHMP/ICH/353369/2013	ICH Q3D “Elemental impurities”
EMA/CVMP/QWP/153641/2018	Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products
CPMP/QWP/4359/03 EMEA/CVMP/205/04	Guideline on plastic immediate packaging materials.
EU regulation 10/2011 (and subsequent amendments)	Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.
CPMP/QWP/122/02 EMEA/CVMP/846/99	Stability testing of existing active substances and related finished products.
CPMP/ICH/420/02	ICH Q1E “Evaluation of stability data”
EMA/CVMP/VICH/858875/2011	VICH GL51 “statistical evaluation of stability data”
CPMP/QWP/609/96	Declaration of Storage Conditions: in the product information of Medicinal Products and for Active Substances

EMEA/CVMP/422/99	Declaration of Storage Conditions: In the product information of pharmaceutical veterinary medicinal products and for active substances
EMEA/CHMP/CVMP/QWP/850374/2015	Guideline on sterilisation of the medicinal product, active substance, excipient and primary container
EMA/CHMP/CVMP/QWP/496873/2018	Guideline on the quality of water for pharmaceutical use

Questions and Answers (EMA, QWP, ICH)	
EMA/CHMP/CVMP/QWP/152772/2016	Quality Working Party questions and answers on API mix
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-1	How should the quality of a starting material of herbal origin be controlled when it is used to manufacture a semi-synthetic active substance?
EMA/409815/2020	Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products
ICH Q11 Q&A	Questions and Answers: selection and justification of starting materials for the manufacture of drug substances

WHO Technical Report Series	
No. 1010, 2018	Annex 10: WHO guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products