Certification of Substances Department

FML/CB

PUBLIC DOCUMENT
(LEVEL 1)
English only

PA/PH/CEP (04) 1, 6R

Strasbourg, December 2018

Certification of suitability to Monographs of the European Pharmacopoeia

CERTIFICATION POLICY DOCUMENT
Content of the dossier for chemical purity and microbiological quality

Implementation	January 2019

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CONTENT OF THE DOSSIER FOR A SUBSTANCE FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY EVALUATION

This document is intended for applicants as a guide for compiling a dossier that is suitable for evaluation for a Certificate of Suitability (CEP).

A new CEP application should contain three modules (Modules 1 – 3). Module 1 should contain a cover letter, correctly filled application form including relevant declarations and information on the expert (i.e. CV). Module 2 (Quality Overall Summary (QOS)) should be prepared preferably by using EDQM template for QOS. Module 3 should be structured according to CTD as defined by ICH guidance documentation (ICH M4 *Organisation of the common technical document for the registration of pharmaceutical for human use*). For further details please use the EDQM *Guidance for electronic and paper submissions for Certificates of Suitability (CEP) applications* (PA/PH/CEP (09) 108).

The application form, relevant annexes and the QOS template can be downloaded from the EDQM website (https://www.edqm.eu).

In this policy document references to guidelines are inserted to assist applicants. It remains the applicant's responsibility to ensure that all relevant legislation and guidelines, as revised or maintained, are respected in the application when applicable. The guidelines referenced in each section provide useful information on the content expected in that section. However, this list should not be regarded as comprehensive. The requirements of the European Pharmacopoeia (Ph. Eur.) general monographs *Substances for Pharmaceutical Use* (General Monograph 2034), *Products of Fermentation* (General Monograph 1468) and *Products with risk of transmitting agents of animal spongiform encephalopathies* (General Monograph 1483) should be respected in the application, when applicable.

This policy document applies to all substances described in the Ph. Eur. and that are suitable for a certificate of suitability. This includes substances where the manufacturing process is developed on the bases of a traditional approach, an enhanced approach or combination of both. In situations where Quality by Design has been utilised and a design space has been claimed the information in sections 3.2.S.2.2-2.6 should be prepared and organized according to ICH Q11 *Development and Manufacture of Drug Substances* (and ICH Q8 *Pharmaceutical Development*, ICH Q9 *Quality Risk Management* and ICH Q10 *Pharmaceutical Quality System* as applicable) and the related EMA/ICH questions and answers documents which give additional guidance as needed.

Module 1

Commercialisation history of the substance:

Applicants for a CEP should summarise the licensing history for medicinal products licensed in Europe that contain the substance made by the applicant (or manufacturer if different) in accordance with the currently proposed method of manufacture, naming the countries, products and commercialisation dates. It should be made clear if the products are for veterinary use only. Information on the Active Substance Master Files (ASMF) submitted to the EMA and/or National Licensing authorities should be supplied. This information should be given in the relevant sections of the application form.

Declarations:

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

Each manufacturer involved in the manufacturing process from the introduction of starting material(s) to the final substance should be listed and appropriate declarations should be submitted. If the manufacturer is different to the holder then it is the address of the manufacturer that should be recorded on the declaration(s).

The following declarations should be provided:

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

- A signed declaration from the manufacturer that manufacture is conducted in accordance with the presented dossier and that GMP which complies with *Vol. 4 of the Rules Governing Medicinal Products in EU* is applied for each manufacturing step from the introduction of the starting materials. If available, a copy of a GMP certificate should be supplied. For excipients, other approaches to GMP are acceptable, if justified.

- A signed declaration that the manufacturer is willing to be inspected, in accordance with the relevant legislation, before and/or after being granted a certificate of suitability. When the proposed holder is not the manufacturer this declaration should also be provided by the proposed holder, together with a declaration from the final substance manufacturer committing them to keep the proposed holder informed of any changes to the documentation so that this may be declared to the EDQM.

B) For the holder:

- A declaration on the use/non-use of material of animal or human origin during manufacture. Where materials of animal or human origin are used in the process, this will be mentioned on the certificate. In this case, CEP holders and marketing authorisation holders should be aware that viral safety data are to be submitted in the marketing authorisation application for the finished medicinal product. 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).

- The applicant should also provide a commitment to provide samples of the final substance and/or its impurities to the EDQM if requested.

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 national competent authorities of the Ph. Eur. Member States and the European Medicines Agency (EMA) including EMA committees and working parties/groups and the members and experts thereof.

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) - (see Eudralex – *Notice to applicants and regulatory guidelines medicinal products for human use, Presentation and format of the dossier, Volume 2B*). It is expected that the Quality Overall Summary (QOS) discusses the ability of the European Pharmacopoeia monograph to control the quality of the final substance, and in particular the potential in-house impurities, and the necessity for alternative or additional methods if appropriate. Particular attention should be given to justifying cases where testing for possible impurities is omitted, for example due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.

Module 3

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):

Where more than one grade, in respect of physical characteristics, is produced, the manufacturer may wish to apply for one certificate, which covers all grades, or separate certificates. Where separate certificates are requested, a dossier must be submitted for each certificate and the grade will be mentioned as subtitle on the certificate and this should be made clear on the application form. Examples are: special particle size, micronised or non-micronised grade etc. In any case, the different qualities shall comply with the general level of quality defined in the monograph. It is optional to have different grades in the sub-title of a certificate if several grades are claimed; this should be made clear on the application form. The possibility for one certificate to cover different grades cannot be accepted when these different grades require different limits and/or methods for the control of impurities; in which case separate certificates will be needed and the relevant grades will be mentioned in the sub-title of the certificate. For grades not described in the European Pharmacopoeia, 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. If more than one grade is described in the same dossier the batch analysis results, in respect of impurity profiles, should be given for all grades.

It should be noted that:

- The use of additives (antioxidants etc.) is only allowed if specifically foreseen by the relevant monograph. If an additive is used then a suitable test method should be provided and validated, and any relevant limits for additive should be included in the specification and should be justified. If a monograph is available then it is expected that the additive complies with its respective monograph. Further information is available in the Quality Working Party (QWP) questions and answers on API-mix and in the EDQM guideline *API-Mix (or mixtures) and CEPs* (PA/PH/CEP (16) 70).

- Acceptable claims regarding sterility/freedom from pyrogens and/or bacterial endotoxins should be indicated and reference given to the relevant test of the monograph (sterility/LAL/pyrogens). It is only possible to introduce grades for freedom from pyrogens and/or bacterial endotoxins on the CEP when the monograph foresees this. Separate applications will be needed if both grades are produced; e.g. non-sterile and sterile, or pyrogenic/bacterial endotoxin-free and non-pyrogenic/endotoxin free substances.

- 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). When granted, the CEP will include the relevant subtitle ("sterile"), it will specify the sterilisation method used and will refer to the test for sterility. It will also be mentioned that the sterilisation process has been assessed and approved.

- With regards the TSE risk, where a raw material used for the manufacture of a 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.

- Multiple polymorphs cannot be described as grades on a single CEP. Separate CEPs can be obtained for each polymorphic form if the monograph does not restrict the polymorphic form.

In the particular case where the monograph covers different grades of the substance it is possible to mention these different grades in the sub-title of the CEP if the specification is within the range of the monograph and also if the monograph states that the label should mention the particular grade.

Grades mentioned in functionality related characteristics are not mandatory unless specifically mentioned in the respective monograph. It is possible to add a sub-title for those characteristics. If a sub-title is requested then a validated method should be provided along with an appropriate limit(s).

Manufacture (3.2.S.2)

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

Names and addresses of each manufacturer involved in the manufacturing process from the introduction of starting material(s) to the final substance should be listed in the application and their role explained.

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

Applicants are reminded that the requirements of the Ph. Eur. General Monograph 1468, *Products of Fermentation and* Ph. Eur. General Monograph 1483, *Products with risk of transmitting agents of animal spongiform encephalopathies* should be respected when applicable.

Where materials described in the European Pharmacopoeia are introduced into the process, typically as intermediates or starting materials, where these materials are covered by a CEP, the CEP can be provided. 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 supplied:

— An outline or flow diagram, including the structural formula for the starting materials and all intermediates, accompanied by all solvents, reagents and catalysts 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.

— Detailed description of each stage of the manufacture, including information on solvents and reagents, catalysts, conditions of reactions, information on intermediates, which are 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 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 can be granted provided scale-up is reported to the EDQM. 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 sub-title may need to be submitted for each alternative process.

The cases where routine reprocessing is carried out should be identified and justified. Any data to support this justification should be either referenced or presented in the application. The reprocessing method should be clearly described and the criteria for deciding when re-processing can be performed should be provided.

Normally re-working (application of steps different from those of the process) is not acceptable since this implies the use of different solvents, which leads to a change in the specification, and /or impurity profile of the substance.

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

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):

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, the ICH Q11 Questions and Answers*: Selection and Justification of Starting Materials for the Manufacture of Drug substances,* and the EMA *Guideline on the chemistry of active substances* (EMA/454576/2016).

Generally, a flow chart of the synthesis of the starting material(s) should be provided, including the solvents, reagents, catalysts etc. The starting materials should be fully characterised and a complete and justified specification should be provided including limits for impurities such as specified, unspecified and total impurities, solvents and reagents as needed. Descriptions of analytical methods or a reference to a pharmacopoeial method should be provided.

Control and absence of carry-over of potential impurities (unchanged or as 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) should be declared and where more than one supplier is used then batch analyses results from the final substance manufactured from the different sources of starting material should be given.

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 fermented or extracted starting material should be well characterised, and in addition to typical impurity discussion (as mentioned above) the possibility of fermentation specific impurities (e.g. DNA, proteins etc.) from the fermentation process to the final substance should be discussed and similarly, carry-over of herbal related impurities such as pesticides, fumigants, elemental impurities, aflatoxins etc. should be discussed, 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 true products of fermentation, and consequently the declared starting material should be the producer strain.

Other raw materials

An appropriate specification and description of the analytical methods should be provided for each raw material and solvent used in the production. For solvents and key reagents it is expected that the specification contain at minimum identification, assay, and control of impurities. The closer to the final substance the more detailed impurity control should be considered. Control of class 1 solvents as potential contaminants in relevant solvents should be taken into consideration, especially for solvents used in the purification steps.

If materials are recycled then justified specifications for the recycled materials should be supplied.

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

Any critical steps should be identified. Tests and acceptance criteria performed at the critical steps should be provided. In-process controls should be described.

A suitable and detailed specification is expected for each isolated intermediate, along with analytical methods descriptions. The specification should generally be justified and information on the impurities found in isolated intermediates during manufacture should be included (e.g. specified, unspecified or total impurities) as necessary.

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

Process validation and/or evaluation studies shall 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 GMP Part II is applicable to the manufacture of an active substance (API) till the point immediately prior to the sterilisation of the API. Sterilisation and aseptic processing should be performed according to EU GMP Annex I (Volume 4 of Eudralex).

CEP holders and Marketing Authorisation holders should be aware that the sterilisation of the final substance is considered as an intrinsic part of the manufacturing process of the medicinal product. Consequently, in addition to the CEP, full data on the sterilisation must be provided in the marketing application for a medicinal product, even if these data have been submitted in the CEP application.

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 then compliance is expected at the time of submission and the requirement is

part of the evaluation procedure. However, no data are expected from the applicant if the production statement for a particular substance refers to specific biological requirement e.g. *the substance is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure,* but this will be mentioned on the certificate as this requirement is addressed by national authorities during evaluation of marketing authorisation application and not by the EDQM.

Where substances are manufactured by enhanced approach (Quality by design) then appropriate data should be provided and presented under relevant sections including 3.2.S.2.5.

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

As stated in the Ph. Eur. General Notices (10000) and *Summary of requirements for active substances in the quality part of the dossier* (CHMP/QWP/297/97) 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 suitable reference standard is not available then appropriate characterisation should be submitted.

Impurities (3.2.S.3.2)

It is expected that a detailed impurity discussion is provided, and this concerns not only related substances but all potential impurities stemming from the manufacturing process such as reagents, solvents, catalysts, by-products and other raw materials. If the monograph does not contain a suitable test to control these potential impurities then it is expected that discussion and demonstration of absence or control are given with specific attention to materials used in the last steps of synthesis. The analytical methods and minimum validation data should be provided, including suitability and LOD/LOQs (reported in ppm with regards the final substance where possible).

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.

Possible impurities originating from the route of synthesis or from degradation should be listed and discussed with an indication of their origin (starting material, reagent, solvent, catalyst, intermediate, degradation product). 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 found above the relevant reporting threshold or the disregard limit of the monograph it must be demonstrated whether the monograph controls

them and where applicable retention times, correction factors and limits of detection and quantification should be provided. If the monograph does not 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 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) their limits should be established according to the related substances section in the Ph. Eur. General Monograph 2034*, Substances for Pharmaceutical Use*. Impurities found above the relevant identification threshold should be identified and for impurities present above the relevant qualification threshold, these should be qualified and where necessary toxicological data should be supplied. Alternatively, and where appropriate, it may be demonstrated by other means that the impurity profile (number, nature, amount) of the substance is comparable to that of products already on the market.

For substances out of scope of the Ph. Eur. General Monograph 2034*, Substances for Pharmaceutical Use* and which contain impurities that cannot be controlled by the monograph's criteria for related substances then suitable limits should be proposed and where necessary toxicological data should be supplied. Particular emphasis is given to antibiotics and the provisions laid out in the *Guideline on setting specifications for related impurities in antibiotics* (EMA/CHMP/CVMP/ QWP/199250/2009).

In line with current EU guidance on potential mutagenic impurities (ICH M7) a specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential /mutagenicity. If a mutagenic impurity is liable to be present in the substance then the control strategy should be demonstrated to be in compliance with current EU guidance. Justified control limit should be proposed together with a validated method for determining the content of the mutagenic impurity.

In 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 retest period on the certificate.

If alternative routes of synthesis are described the possible impurities are discussed separately for each route.

<u>Other impurities</u>:

Residues of residual toxic reagents should also be discussed and where applicable a suitable limit and test method should be proposed if the monograph does not provide a suitable test.

Residues of acids or bases that are not mentioned in the ICH guideline for residual solvents (e.g. HCl, organic acids) should also be discussed if the monograph does not provide a suitable test (pH, acidity or alkalinity).

Residual solvents:

The Ph. Eur. general chapter 5.4 *Residual Solvents* is to be applied. In addition, the Annexes to: *Impurities: Guideline for Residual Solvents* (CPMP/ICH/283/95) and *Guideline on Impurities*: *Residual Solvents* (CVMP/VICH/502/99) *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 the exemption of a test. 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 general chapter, class 1 solvents should not be employed in the manufacture of active substances or excipients. If used, there needs to be a clear benefit/risk justification provided. The justification should in general demonstrate the need for class 1 solvent as a solvent (not applicable when it is a reagent) in the manufacturing process by comparing the relative substance(s) manufactured with and without the class 1 solvent. The final decision on the acceptability of the use of a class 1 solvent during manufacture will be taken by the Technical Advisory Board.

Any limit higher than the ICH option 1 limit should be justified by batch data and according to an option 2 calculation, i.e. based on the maximum daily dose (for class 2 solvents only).

Low toxicity solvents (Class 3) can be limited by a test for Loss on drying with a limit of not more than 0.5%. If the limit in the loss on drying test of the monograph is more than 0.5% then generally 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 for the substance covered by the CEP. The applicant may choose to provide or not to provide a risk management summary (RMS), as described in ICH Q3D *Elemental Impurities* and the EDQM guideline *Implementation of ICH Q3D in the Certification Procedure* (PA/PH/CEP (16) 23). This guideline also clarifies what is necessary where elemental impurities are intentionally introduced in the manufacture of the final substance.

Control of Drug substance (3.2.S.4)

Specification (3.2.S.4.1):

The specification should be in accordance with the current general and specific European Pharmacopoeia monographs. Where the monograph has been shown not suitable to control the quality of the substance and in particular the related substances, then additional analytical methods should be identified. Any additional tests to those of the monograph shall be justified.

Where the monograph includes a Production section the requirements of this section should be respected in the application. For chemical or analytical production requirements the applicant should provide discussion and appropriate method/data to allow for evaluation. If the requirement is biological in nature this is not evaluated by EDQM and a statement is added to the CEP alerting users to that fact.

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

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 since the current monograph is viewed as insufficient and therefore the manufacturer may also wish to take it into consideration in the application. 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). They would be appended to the certificate only if shown to be needed as supplementary to those of the monograph (when shown insufficient).

Monographs describing a TLC method to control related substances are generally 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* and 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 one of the Ph. Eur.

To facilitate the preparation of the certificate a separate description of any supplementary tests should be presented.

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 their 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 and cross validated with reference to the monograph's method(s). At the minimum

comparison of three batches is expected with appropriate impurity spiking in situations where the substance is very pure.

If a method is exactly as described in the general methods of the European Pharmacopoeia (i.e. general method 2.4.24 for residual solvents) a full validation is not required but the method should be described and only 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 Ph. Eur. member state do not have to be fully validated (though specificity and level of detection and/or quantification should be calculated). 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).

Batch analyses (3.2.S.4.4):

Batch results of full testing of at least three batches should be given and should comply with the monograph. Results below 1.0 % for related substances should be reported with two decimal places e.g. 0.25 %. When different sources of starting materials, different grades, methods of manufacture or alternatives or different sites are described in the dossier, the results of analysis of the batches shall be provided for each of them. The batch size and the date of manufacture and analysis should be given. The results of analysis should be given as actual figures whenever possible instead of statements such as "conforms", "complies" etc.

The batch size should in general be in accordance with the declared batch size range as specified in the description of the manufacturing process.

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 (metal catalyst/reagent/solvent) but which is not used during manufacture, the manufacturer may omit the test in the specification which should be made clear in the dossier. If the proposal of the applicant is accepted, a clear 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 have to be suitably described (in terms of identification, purity, assay, etc.) and their establishment has to be 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 (primary and secondary packaging) and the specification (including description and identification (e.g. IR)) should be supplied. Where relevant, conformity to the relevant Ph. Eur. monographs and the EU note for guidance *Plastic Primary Packaging Materials* (CPMP/QWP/4359/03 and EMEA/CVMP/205/04), should be shown. 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.

For non-plastic container-closure systems, their suitability should be discussed with respect to choice of materials, protection from light and/or moisture, compatibility with the substance and/or any safety aspects along with reference to stability data that can support the suitability of the proposed container-closure system.

Stability (3.2.S.7)

As stated in the EU note for guidance *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02 and - EMEA/CVMP/846/99), for final substances described in an official European Pharmacopoeia monograph which covers the degradation products, results from formal stability studies are not necessarily required. However, when a retest period is requested to be mentioned on the certificate (which is encouraged and it should be made clear on the application form) it should be determined in accordance with the EU note for guidance *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 for Medicinal Products Particulars and 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 retest period and in accordance with the note for guidance shall be supplied.

The information and recommendations given under the heading "Storage" in the Ph. Eur. monograph does not constitute a requirement and are given for information (see Ph. Eur. General Notices). For storage conditions such as "store between 2-8°C" it is not sufficient to reference the statements mentioned in a specific monograph. The applicant should therefore justify the proposed storage conditions by submitting stability data, and precautionary storage conditions are not taken into account. If no request to mention a retest period on the certificate is made, stability data, which should be summarised, may still be submitted, in particular to support the discussion on impurities.

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 Note for guidance *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 retest 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.

References

List of referenced policy papers and guidelines

EDQM Guidelines	**Title**
PA/PH/CEP (09) 108	Guidance for electronic and paper submissions for Certificates of Suitability (CEP) applications.
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.

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

EU/ICH Guideline	**Title**
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 guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities).
EMA/CHMP/ICH/167068/04	ICH guideline Q8 Pharmaceutical development.
EMA/454576/2016	Chemistry of active substances (chemistry of new active substances)
Eudralex	Vol. 4 of the Rules Governing Medicinal Products in EU (e.g. Annex 1 Sterile Medicinal Products).
CHMP/QWP/297/97	Summary of requirements for active substances in the quality part of the dossier
EMA/CHMP/ICH/24235/2006	ICH guideline Q9 on quality risk management.
EMA/CHMP/ICH/214732/2007	ICH guideline Q10 on 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
CPMP/ICH/283/95/ CVMP/VICH/502/99	ICH guideline Q3C 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
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	Evaluation of stability data.
EMA/CVMP/VICH/858875/2011	VICH GL51: statistical evaluation of stability data

EU (EMA, QWP) Questions and Answers
Quality Working Party questions and answers on API mix
How should the quality of a starting material of herbal origin be controlled when it is used to manufacture a semi-synthetic active substance?

ICH Questions and Answers
ICHQ11 Questions and Answers