EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Department

AMEL/CB

PUBLIC DOCUMENT
(Level 1)

PA/PH/CEP (23) 54, draft 4

Strasbourg, May 2024

Certification of suitability to the Monographs of the European Pharmacopoeia

Content of the dossier for sterile substances

Submission to the Technical Advisory Board (Chemical) for agreement	Draft 1	17th October 2023
Submission to CHMP/CVMP QWP for comments	Draft 2	November 2023
Submission to the Technical Advisory Board (Chemical) for agreement	Draft 3	February 2024
Agreement by the Technical Advisory Board (Chemical) by correspondence	Draft 4	March 2024
Submission to the Steering committee	Draft 4	April 2024
Adopted by the Steering Committee for consultation by correspondence	Draft 4	May 2024
Public consultation	Draft 4	May 2024

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1. Introduction

This document is intended for applicants as a guide for compiling a dossier in order to obtain a Certificate of Suitability (CEP) for a sterile substance.

In this policy document references to guidelines are included to assist applicants. It remains the applicant's responsibility to ensure that all requirements and recommendations, as revised or maintained, are respected.

It is possible to apply for a CEP for a sterile substance in the following conditions:

- The substance shall be sterile and shall comply with the *test for sterility* 2.6.1 described in the European Pharmacopoeia.
- The sterilisation process shall be described in detail in the CEP application, together with full data on the validation of the sterilisation method.
- The manufacturer of the substance shall refer to suitable GMP rules. The *Good Manufacturing Practice for Active Pharmaceutical Ingredients* (ICH Q7A) only applies to the manufacture of sterile active substance up to the point immediately prior to the substance being rendered sterile. The sterilisation and aseptic processing of sterile substances are not covered by this guideline and shall be performed in accordance with EU GMP for medicinal products (Commission Directive 2003/94/EC of 8 October 2003, laying down the principles and guidelines of good manufacturing practice for medicinal products for human use and investigational medicinal products for human use, or equivalent), including Annex 1. Declarations referring to appropriate GMP covering the sterilisation steps and subsequent aseptic handling should be provided.
- Unless evidence is provided that the manufacturing site(s) involved in the sterilisation and aseptic handling of the sterile active substance is subject to routine inspections by a EU regulatory authority, and a valid GMP certificate in compliance with the EU GMP rules Part I and Annex 1 has been issued covering the substance subject of the CEP application, the manufacturing site(s) involved will be inspected by the EDQM (fee for inspection will also apply).
- If both sterile and non-sterile substances are produced, separate CEP dossiers shall be submitted and separate CEPs would be granted.
- The application form for the sterile substance should specify that the substance is sterile (as a subtitle). Additional fee for assessment of the sterilisation data will be required.

It should be noted that sterilisation of the active substance is generally regarded by the licensing authorities as part of finished product manufacture. Therefore, data on the sterilisation process of the active substance (including validation data) should be shared with the Marketing Authorisation applicant/holder for inclusion in the marketing authorisation application for the finished product submitted to the relevant licensing authority(ies).

2. Scope

The acceptability of CEP applications for sterile active substances is applicable to the manufacturing processes where sterilisation operations required to obtain the sterile material are performed either at the active substance manufacturing site or at a different site.
The CEP holder is responsible for the manufacturing steps to obtain the active substance and its sterilisation, and full documentation should be provided in the CEP application.

This guideline should be read in conjunction with the current EDQM policy "Content of the dossier for chemical purity and microbiological quality", the EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374), the Ph. Eur., chapters 5.1.1 *Methods of preparation of sterile products* and 5.1.2. *Biological indicators and related microbial preparations used in the manufacture of sterile products*, the Annex 1 of Eudralex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.

3. Documentation to be provided for the sterile substance

The applicants are expected to provide relevant information about the sterile aspects of the manufacturing process in section 3.2.S.2.5.

Justification for method of sterilisation

In most cases, the sterile substance is manufactured by sterile filtration. The substance in solution should be sterilised by filtration through a sterile filter (with a nominal pore size of a maximum of 0.22 µm) and subsequently aseptically filled into a previously sterilised container.

Substances may occasionally be rendered sterile by dry heat sterilisation, by the use of ionising radiation or by the use of ethylene oxide gas. The use of these methods should be adequately justified taking into account the *Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container* (EMA/CHMP/CVMP/QWP/850374).

When aseptic preparation/sterile filtration is used, the following information related to the sterilisation process is expected to be reported in the dossier:

Manufacturing Process

Manufacturing areas

The manufacture of sterile substances should be carried out in appropriate cleanrooms.
Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions and to minimize the risk of microbial and particulate contamination.

The manufacturing area grades for each of the production steps which lead to the packaged sterile substance (e.g. solution preparation and filtration, filling into final containers, etc.) should be in compliance with Annex 1 of of Eudralex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. The relevant information should be included in the dossier.

Summary of manufacturing process related to sterile filtration/aseptic processing

Adequate narrative and schematic description of the steps which lead to the sterile active substance in its final container is expected. (i.e. solvents, temperature, equipment, pre- and sterile filtration, crystallisation, seeding, centrifugation, isolation, size reduction, blending of sub-lots, freeze drying, drying, filling in containers).

The manufacturing batch size should be stated in the CEP application. If alternative batch sizes or a variable batch size are described, validation of the sterilisation process should be undertaken on the maximum manufacturing batch size.

Information on filters used

The filters used for non-sterilising and sterilising filtration should be identified and described in sufficient detail. Type of material, nominal pore size and number of filters should be stated. For the sterilisation filters, the filter area should be indicated.

Information on filtration conditions and parameters should be included (maximum proposed duration of filtration, maximum volume filtered, maximum duration of use of filters, maximum duration of campaigns, operation pressure, etc.).

Confirmation should be provided that the integrity of the filters is tested both before and after filtration. Method used for filter integrity test should be described and validated. Acceptance criteria for integrity testing before and after sterile filtration should be established. It should be indicated which measures will be taken in case of failure.
Test certificates from the suppliers should be provided for the filters used.

Validation of the filters used

The non-sterilising and sterile filters should be validated as follows:

Microbial challenge test data are expected, to confirm the suitability of the sterilising filters. The test should be performed product related with a minimum of 10^7 CFU/cm^2 using a justified indicator organism. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test.

Potential absorption of solution components to the filters used (non-sterilising and sterilizing filters) should be investigated with the product to be filtered.

Filter compatibility under worst case conditions and potential extractables/leachables for all non-sterilising and sterilising filters including those for the solvent line should be investigated. It should be proven that no toxicologically relevant amounts of extractables or leachables are released from the filters into the filtered solution.

Sterilisation of filters and processing equipment

Information on the sterilisation of the filters and processing equipment in line with Annex 1 of Eudralex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use of should be reported.

Pre-filtration Bioburden

A limit should be set for the bioburden of the bulk solution immediately prior to sterile filtration.
A limit of NMT 10 CFU/100 ml (TAMC) is normally acceptable. If a pre-filter is added as a precaution only and not because the unfiltered bulk solution has a higher bioburden, this limit is applicable also before the pre-filter and is strongly recommended from a GMP point of view. A bioburden limit of higher than 10 CFU/100 ml before pre-filtration may be acceptable if this is due to starting material known to have inherent microbial contamination. In such cases, it should be demonstrated that the first filter is capable of achieving a bioburden of NMT 10 CFU/100 ml.

The maximum time between the start of bulk solution preparation and sterile filtration should be stated, minimised and appropriately supported by data. Filtration times longer than 24 hours should be justified.

Re-use of filters

Information on whether the prefilters or the sterilizing filters are re-used should be included in the dossier.
The Requirements of Annex 1 of Eudralex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use should be considered.

Aseptic processing

The final processing of the material may include blending of sub-lots (provided testing of such sub-lots for critical quality parameters is performed) and milling, in addition to filling into final containers.
The immediate containers used for the filling of the bulk material should be sterile. The relevant information should be included in the dossier.
Information on the bulk holding time before filling and on the filling time should be stated and appropriately supported by data. The times should be minimised. Holding and filling times longer than 24 hours should be justified and supported by a risk assessment.

Process Simulation / Validation

As a standard, details of three recent consecutive media fill runs performed under worst case conditions with an appropriate sterile nutrient medium and/or a justified surrogate for the substance should be included together with a copy of the protocol. It should be outlined how the media fill trial mimics the routine manufacturing process. The target should be zero growth. Any contamination should be investigated.
Documentation should be provided to demonstrate the validation of the aseptic manufacturing process.
Information on the frequency of the media fill runs performed should be stated. Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process.
The requirements of Annex 1 of Eudralex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use should be considered.
The proposed holding and processing times should be covered by the media fill runs.

Sterilisation of Packaging

Details are required of the methods used to sterilise the packaging components. If the reference conditions of the Ph. Eur., 5.1.1 are not used, validation data for the sterilisation process of the packaging material should be provided. The requirements of the *Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container* (EMA/CHMP/CVMP/QWP/850374) should be considered to determine the most appropriate method of sterilisation of the packaging components.

The integrity of the packaging once filled with the sterile grade material should be validated.
If a re-test period is claimed, results of stability studies are required as an assurance that sterility is maintained in the container.

Re-test Period

If the applicant requests a re-test period, the stability study should include sterility testing at the end of the proposed re-test period. The stability study should be undertaken in packaging that is the same as, or simulates, the commercial packaging.

List of referenced documents

EDQM Guidelines	Title
PA/PH/CEP (04) 1	Content of the dossier for CEP applications for chemical purity and microbiological quality of substances for pharmaceutical use

Ph. Eur. texts	Title
Chapter 2.6.1	Sterility
Chapter 2.6.14	Bacterial endotoxins
Chapter 5.1.1	Methods of preparation of sterile products
Chapter 5.1.2	Biological indicators and related microbial preparations used in the manufacture of sterile products

EU/EMA/ICH Guideline	Title
Eudralex Volume 4, Annex 1	EU Guidelines for Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Manufacture of Sterile Medicinal Products
EMA/CHMP/CVMP/QWP/850374	Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container