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Certification of suitability to the Monographs of the European Pharmacopoeia

CONTENT OF THE DOSSIER FOR A SUBSTANCE FOR TSE RISK ASSESSMENT

Addresses	Role	Date
TSE TAB	Adopted by correspondence	September 2017
Steering Committee	Adopted by correspondence	December 2017

Address: 7 Allée Kastner, CS 30026 F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

This document is intended for applicants as a guide for compiling a dossier that is meant to be evaluated to get a Certificate of Suitability (CEP) for a material likely to present a TSE risk. The scope is to demonstrate compliance of the material to the Ph.Eur. General Monograph 1483 on Products with risk of transmitting animal spongiform encephalopathy agents and the Ph.Eur. General Chapter 5.2.8 Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. The procedure is also applicable to raw materials intended to be used in medical devices.

A new CEP application should contain three modules (modules 1, 2 and 3). Module 1 should contain a cover letter, a duly filled in application form including relevant declarations. Module 2 should contain the expert report and the CV of the expert in charge of the dossier and module 3 should be structured with reference to policies and guidelines listed in Annex 1, including the relevant information as detailed below.

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 amended, are implemented in the application.

Module 1

The application form should be prepared by filling in all the sections of the template available on the EDQM website (http://www.edqm.eu).

Signed declarations with regard to the quality control system(s) in place (i.e., GMP, ISO 9000, HACCP, etc.) should be provided covering the applicant as well as any other manufacturer involved in the manufacturing process of the material. With regard to gelatin the implementation and respect of HACCP procedures is strongly recommended.
The same entities should also declare willingness to be inspected by relevant Authorities with reference to the quality system(s) in place and to the submitted dossier. The same information with regard to the quality assurance systems in place should be given in both the dossier and in the application form.

Module 2

A critical evaluation of the content of the dossier should be given in Module 2 in the form of an expert report. The expert report should discuss the ability of the system in place to minimize the risk of TSE for the substance with reference to the Ph.Eur. General Chapter 5.2.8. The Curriculum Vitae of the expert in charge of the dossier and of the expert report is also expected in Module 2. The CV should highlight the experience of the expert in this field.

Particular attention should be paid to justifying cases where the information given differs from that requested in the Ph.Eur. General Chapter 5.2.8.

Module 3

The Module 3 contains the Dossier that should be structured as detailed below.

1. GENERAL INFORMATION

1.1 Nomenclature

The dossier should cover one product with the possibility to cover grades of the same product. The proposed name of the material should follow where possible official nomenclatures (i.e. defined by IUPAC, INN, European Pharmacopoeia, etc.). The name should be meaningful in the context of the dossier and it should allow a clear and unambiguous identification of the material. If manufacturer's codes or catalogue numbers allow distinguishing between the different grades of the product they may be proposed as sub-title of the certificate. Brand names are generally not acceptable and should only be used when no other way to identify a material is available and they will only be introduced in the sub-title.

1.2 Details of manufacturers

Complete names and addresses of intended holder of the Certificate of Suitability, manufacturers and manufacturing sites should be given in the dossier.

If other parties are involved in certain stages of the process, details of their involvement and of other site addresses must be provided and information given on the contractual arrangements regarding sole or shared responsibilities. If several sites are used (eg. to provide alternative capacity), it should be established that all measures put in place are transposed to all sites, particularly as regards supply of raw materials, production process, quality assurance system and traceability.

1.3 History of the product

The length of time that the substance has been produced according to the presented dossier and the length of time that the substance is on the market should be clearly reported in the dossier. Information on licensed products containing the substance as ingredient or where the substance is used in the process should be given, including details on the countries (inside and outside Europe) where the material is commercialised.

2. ORIGIN OF RAW MATERIAL AND TYPE OF TISSUE USED

Detailed information on the following is required as described in the general chapter of the Ph. Eur. 5.2.8..Any deviation is to be discussed and justified in the dossier and in the expert report.

2.1 Geographical origin

The geographical origin (country of origin) of animals used to source organs, tissues and organic material in general should be clearly stated in the dossier. The OIE system for classification of the geographical BSE risk is to be used as reference. The actual status of countries is published by OIE (http://www.oie.int/en/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/). Animals should be sourced from countries with the lowest possible BSE risk (Category A) unless other factors (e.g. using tissue with no detectable or lower infectivity or a prion reducing manufacturing process) justify sourcing from countries with controlled BSE risk (OIE Cat B). Any justification in support of the choice of countries of origin should be given in the dossier. As a general principle, animals should not be sourced from countries with an undetermined BSE risk (OIE Cat C) except for specific materials identified in section 6 of Ph. Eur. 5.2.8. Apart from this general principle countries with an undetermined BSE risk might be acceptable for certification after a justification which should be given in the dossier. The materials should be subject to processing conditions which are as rigorous as those are given in section 6.4 (tallow derivatives), 6.5 (animal charcoal), 6.7 (wool derivatives) or 6.8 (amino acids). Other justification than rigorous processing conditions is only acceptable in exceptional circumstances. If available, evaluations of the Geographical BSE Risk (GBR) issued by the former Scientific Steering Committee of the EU Commission should be referred to (countries that still do not have an OIE status).

No specification of the country of origin is necessary for tallow derivatives, milk and milk derivatives, animal charcoal, and amino acids, which are considered compliant if the specific conditions outlined in Ph. Eur. 5.2.8 are met. Evidence should be given in the dossier.
The origin of sheep is not relevant for wool and wool derivatives fulfilling the conditions outlined in section 6 of Ph. Eur. 5.2.8. Evidence should be given in the dossier.

A statement "All EU countries" is sometimes proposed, based on the fact that there is free trade of cattle within EU countries and therefore the designation of the original country for an animal could be difficult, since the animal could be raised in one country and slaughtered in another one. The TSE TAB concluded that there are no particular risks with this statement (which is therefore acceptable), except for blood derivatives and material intended to be used in medical devices. The acceptability of the statement "all EU countries" is part of the evaluation performed by the EDQM.

2.2 Type of tissue used

The type of tissue used should be listed in the dossier. Animal tissues have been classified in 2006 into 3 risk categories by the WHO and this classification can be found in the annex of Ph. Eur. 5.2.8.
Certificates of suitability cannot be granted for material from Cat IA (high infectivity) tissues.
The ways of obtaining the different tissues and the age of animals should also be stated in the dossier. The relevance of providing a full description of the collection of tissues depends on the particular application and a justification should be given in the dossier.

An age limit of 30 months has been set for peptones from OIE Cat B countries. In addition the age of cattle is relevant in specific cases for bovine bone gelatin, bovine blood and blood derivatives (see section 6 of Ph. Eur. 5.2.8) and for raw materials intended to be used in medical devices (see below). Where age is a relevant factor, it should be clarified in the dossier how the age of animals is verified by the manufacturer or/and by the supplier of tissues.

If relevant, it should be stated that animals from which the raw material is derived is fit for human consumption. Relevant certificates (i.e. veterinary certificates) should be given in the dossier.

Slaughtering techniques should be described in the dossier, including the way "specified risk material" (SRM) such as skulls, vertebrae and spinal cord is removed. Attention should be paid to the description of the procedures in place to reduce the risk of cross-contamination during collection of the material of interest. Background information can be found in the EFSA assessment from 2004 (http://www.efsa.europa.eu/fr/efsajournal/pub/123).

In particular:

- For gelatin and collagen produced from bovine hides it should be clarified how the risk of cross contamination of hides is minimised (especially if hide from the head part is included);
- For bovine bone derived gelatin it should be clarified in the dossier whether skulls, spinal cord and vertebrae are removed during the collection of bones. The requirements set by the Ph. Eur. 5.2.8 should be met.
- For bovine blood and blood derivatives reference is made to section 6 of Ph. Eur. 5.2.8;
- For tallow derivatives, amino acids, charcoal and when the part of animals used is not known: these substances can be considered compliant if manufacturing conditions outlined in the specific sections of Ph. Eur. 5.2.8 are met. In addition for tallow derivatives, SRM should be excluded as far as possible and the material should be Category 3 or equivalent as defined in Regulation (EC) 1774/2002 (as amended by EC 1069/2009) of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption. Details in the dossier should be given.

3. MANUFACTURING PROCESS

A description of the manufacturing process should be included in the dossier, along with details on reagents used, operational conditions adopted (i.e. times, temperatures, pressures, etc.), in-process controls and limits applied on the controlled parameters. The use of dedicated manufacturing lines should be highlighted in the dossier, if any. The batch size range the process refers to should be specified.

When necessary, indications given in paragraph 3.5 of Ph. Eur. 5.2.8 should be taken into account while describing the manufacturing process in the dossier. Any deviation should be discussed and justified in the dossier.

Procedures in place to avoid any possible source of contamination with other material of TSE relevant species during the manufacturing process should also be described.

4. TRACEABILITY

The system in place to ensure traceability should be described in the dossier. Traceability of raw materials used in the process, intermediates and final product should be discussed.

If any, code numbering systems used to distinguish different products and/or batches produced in the same manufacturing site should be given in the dossier.

5. AUDITING SYSTEM

The systems in place for auditing the raw material suppliers, frequency and points of control should be given in the dossier, including acceptance criteria. Copies of SOPs and auditing schemes can be included in the dossier. It should be stated whether the audits are paper audits and/or on-site audits.
Self-auditing should also be described in the dossier, including SOP's and auditing schemes.
Evidence should be given in the Dossier.

6. RAW MATERIALS FOR MEDICAL DEVICES

Materials intended to be incorporated into medical devices need special consideration with regards to the implementation of the Ph. Eur. 5.2.8.
To guarantee safety of products with regard to the TSE risk, a combination of at least 2 from the 3 following criteria should be met. Evidence in the dossier should be given.

- To have the safest source of material, sourcing should be preferably from Category A. A justification should be given in the dossier to support the need for sourcing from higher risk geography.
- The age of animals should be 30 months or lower (this refers to material from bovine origin).
- The preparation of the material should include a processing step showing significant reduction of the TSE risk.

Annex 1

List of referenced and applicable policy papers and guidelines

Policy paper / Ph.Eur. Monographs	Title
RESOLUTION AP-CSP (07) 1	Certification of suitability to the monographs of the European Pharmacopoeia
Ph.Eur. General Chapter 5.2.8	Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products
Ph.Eur. General Monograph 1483	Products with risk of transmitting agents of animal spongiform encephalopathies