COUNCIL OF EUROPE

PUBLIC HEALTH COMMITTEE

(Partial Agreement)

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RESOLUTION AP-CSP (07) 1

(adopted by the Public Health Committee (Partial Agreement) (CD-P-SP) on 21/02/2007)

Certification of suitability to the monographs of the European Pharmacopoeia (revised version)

The Public Health Committee (Partial Agreement) (CD-P-SP) consisting, for the purposes of the Convention on the Elaboration of a European Pharmacopoeia, of delegations appointed by the Parties to the said Convention, namely the delegations of Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, "the Former Yugoslav Republic of Macedonia", France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom and the European Union,

Considering the implementation of the Procedure for the certification of suitability of monographs of the European Pharmacopoeia adopted on 1 July 1993 by the Public Health Committee (Partial Agreement) (CD-P-SP) in its resolutions AP-CSP (93) 5 and revised on:

- 4 October 1996 Resolution AP-CSP (96) 5,
- 8 May 1998 Resolution AP-CSP (98) 2,
- 22 December 1999 Resolution AP-CSP (99) 4,

Having regard to the decision taken by the European Pharmacopoeia Commission at its session of November 2006 to update and complete the resolution AP-CSP (99) 4;

Has therefore decided to amend the resolution AP-CSP (99) 4 and to replace it by the text attached.

INTRODUCTION

The manufacturer of a substance will be able to provide proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia by means of a certificate of suitability granted by the Certification Secretariat of the European Directorate for the Quality of Medicines (EDQM) (as described in the EU Directives on the Community code relating to medicinal products for human and veterinary use, the CHMP/CVMP guideline on Summary of Requirements for Active Substances and any relevant national regulation (see 7). To apply for a certificate a manufacturer will submit a detailed dossier (refer to the relevant EDQM documents describing the content of the dossiers - see 7) which may contain confidential data.

The procedure is intended to be applied for the assessment of quality with regards to the criteria of the monograph(s) as appropriate.

The certificate of suitability certifies that by applying the relevant monographs of the European Pharmacopoeia, if necessary with an annex appended to the certificate, it is possible to check whether or not the quality of the substance is suitable for use in medicinal products. In other words, it ensures that all possible impurities and contamination from this particular route of manufacture (including source materials) can be fully controlled by the requirements of the monographs.

SCOPE

The following procedure is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European Pharmacopoeia Commission:

- organic or inorganic substances (active or excipients), manufactured or extracted.

- substances produced by fermentation as indirect gene products, which are metabolites of microorganisms, irrespective of whether or not the microorganisms have been modified by traditional procedures or r-DNA technology (see the monograph Products of Fermentation).

- products with risk of transmitting agents of animal spongiform encephalopathies (TSE) (see the monograph Products with risk of transmitting agents of animal spongiform encephalopathies).

The procedure will not be applicable for direct gene products (proteins), products obtained from human tissues, vaccines and blood products and preparations.

The final decision on eligibility of an application for a certificate of suitability for a material of animal origin is taken by the relevant board of the procedure if necessary.

HOLDER OF THE CERTIFICATE

The certificate of suitability will be delivered in preference to the manufacturer of substances intended for pharmaceutical use. In special cases where the holder will not be the manufacturer but an authorised agent, a formal agreement is required (included in the application form; see 7).

PROCEDURE

The procedure for the certification of suitability will consist of the following steps

1. SUBMISSION OF THE DOSSIER

The manufacturer requests a certificate by submitting a copy of a dossier in English (preferably) or French according to the CTD format and including the relevant part of the Quality Overall Summary (QOS), and an application form duly filled in (see 7), together with samples of commercial batches and fees.

The documentation to be provided by the manufacturer is described in specific documents published by EDQM for the evaluation of the chemical purity, for TSE risk assessment, for herbal drugs and preparations (see 7). For products bearing a risk of transmitting animal spongiform encephalopathy agents, and for which a specific monograph exists in the European Pharmacopoeia, the applicant may apply for a certificate concerning the general monograph Products with risk of transmitting agents of animal spongiform encephalopathies as well as for the specific monograph, or may wish only to apply for a certificate concerning the general monograph. Where no specific monograph exists for the concerned substance only the documentation related to the TSE-risk evaluation should be supplied.

In the application the manufacturer shall declare that the manufacture of the substance in question takes place in accordance with the requirements of the EU Good Manufacturing Practice (GMP) for the manufacture of starting materials (see 7) and in accordance with the dossier presented. For products with risk of transmitting agents of animal spongiform encephalopathies where GMP guidelines have not been elaborated, a suitable quality assurance system (such as ISO 9000 and HACCP)[1] assuring in particular traceability and batch consistency should be applied. Furthermore, the manufacturer should declare its willingness to be inspected if so requested by a relevant authority. Also, in the case of an application submitted by an authorised agent, the above declaration should form part of the dossier and, furthermore, the authorised agent should also declare its willingness to be inspected (in the application form; see 7).

2. ACKNOWLEDGEMENT OF RECEIPT

The Certification Secretariat, after having verified that the dossier submitted is complete, sends an acknowledgement of receipt within eight days which constitutes the official record of the request for a certificate of suitability. Once the dossier is received, and if acceptable, the Secretariat has four months to designate two assessors and have the dossier examined and one month to implement the conclusions and, where appropriate, to deliver the certificate of suitability.

3. DESIGNATION OF ASSESSORS

For each dossier, the Secretariat designates two assessors, who are chosen according to their expertise and the dossier to be examined from a list approved by the Certification Steering Committee (according to the “terms of reference”; see 7) and published periodically on the EDQM web site. The assessors sign a confidentiality agreement and a declaration of interests.

[1] HACCP = hazard analysis and critical control point.

The assessors examine the dossier submitted and prepare a report in three parts:

- Report A or "Confidential report". This report includes an exhaustive critical assessment of the data provided and is kept in the confidential dossier for certification of suitability. Report A can be made available, on request to any marketing authorisation body, in the context of an identified medicinal product license application referring to this substance and the manufacturer would be informed at the same time.

- Report B or "request for revision of the monograph", when updating of the monograph is requested, this report contains the information that the relevant Group of Experts of the European Pharmacopoeia needs to update the monograph which has been shown to be inadequate. It is prepared so as not to divulge the confidential information in the dossier. This part of the report shall be sent to the manufacturer prior to its transmission to the expert group concerned.

- Report C or "Comments for the inspectors". This report contains any useful information for an inspection and/or any specific request for inspection and specifies which GMP guidelines/Quality Assurance system are referred to in the dossier when EU GMP requirements do not apply.

4. ASSESSMENT

The assessment will be done by the assessors, assisted by the Certification Secretariat. In case of doubt the relevant Technical Advisory Board (TAB) (status and role defined in Terms of Reference; see 7) is consulted. Such consultation may be requested by the assessors or by the Certification Secretariat.

If toxicological justification is needed, advice will be sought from a toxicologist assessor for this specific question.

If necessary, the assessors or the relevant technical advisory board requests a laboratory evaluation by the laboratory of the EDQM on the sample supplied.

The assessors and, if necessary, the relevant technical advisory board, finally present one of the four conclusions below:

4.1 *The monograph is able to control the quality of the substance and/or the substance meets the criteria of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies.*

Consequently, the certificate of suitability is granted.
As regards the chemical impurities, if necessary, the transparency of the monograph by mentioning the impurity (ies) tested is improved while taking any measures required to protect the confidentiality of the information (industrial property) with the agreement of the manufacturer.
During a subsequent revision of the monograph, the names of known and controlled impurities that do not concern matters of industrial property are published with the agreement of the manufacturer. In the interim period this (these) impurity (ies) is (are) mentioned in the certificate itself.

If, in exceptional cases, the names of one or more impurities, which are not already mentioned in the existing monograph, for confidentiality reasons cannot be published in the European Pharmacopoeia such names need to be given in the certificate.

4.2 *The monograph is not able fully to control the quality of the substance, but the information provided (new, validated, analytical method and/or additional tests) nevertheless guarantees that the quality of the substance is adequately controlled (note: this situation is not applicable for cases of TSE risk assessment).*

Consequently:
The certificate of suitability is granted. In the certificate is given the full text of the additional test and the full list of named impurities including their limits controlled by that test.
With the agreement of the manufacturer the Secretariat asks the relevant Group of Experts of the European Pharmacopoeia to initiate the appropriate revision process to include an adapted test so as to be fully suitable to control the quality of the substance from this manufacturer as well.
If necessary, the transparency of the monograph by mentioning the impurity (ies) tested is improved while taking any measures required to protect the confidentiality of the information (industrial property) in agreement with the manufacturer.
During a subsequent revision of the monograph, the names of known and controlled impurities that do not concern matters of industrial property are published in agreement with the manufacturer. In the interim period this (these) impurity (ies) is (are) mentioned in the certificate itself.
If, in exceptional cases, the names of one or more impurities, which are not already mentioned in the monograph, for confidentiality reasons cannot be published in the European Pharmacopoeia such names need to be given in the certificate.

4.3 *The information supplied is incomplete and does not allow a conclusion.*

The Secretariat requests the missing information on the manufacturing process, material sourcing, starting materials, additional test methods, validation studies, etc. The additional information received will be assessed within twelve weeks and may allow one of these four conclusions.

The certificate of suitability is not granted as long as the information is still incomplete

4.4 *The monograph is not suitable to control the quality of the substance and an agreement on testing methods for (a) given impurity (ies) or an agreement on the TSE risk assessment has not been reached or the information provided (even after several requests) do not demonstrate compliance with the current requirements.*

Consequently:
A justification for the decision not to grant a certificate of suitability will be given. Before rejection the manufacturer will be given the opportunity to present his position during an appropriate hearing with the relevant board.
The licensing authority of the member states of the European Pharmacopoeia Convention is immediately informed in confidence of this decision in every case where the decision is taken for non-administrative reasons.

5. NOTIFICATION OF THE DECISION

The Certification Secretariat takes the necessary measures to implement the decisions of the assessors, and the relevant technical advisory board when necessary, within 4 weeks.

6. FOLLOW UP TO CERTIFICATION OF SUITABILITY

6.1 Failure to comply with the following will render the certificate void:

6.1.1 Any change (administrative or technical) that may or may not affect the quality, safety or efficacy of the substance, must be reported to the Certification Secretariat of the EDQM so that the dossier can be reassessed and updated.

These changes are classified as notification, minor and major according to the impact on the quality, safety or efficacy of the substance. Special considerations apply to products with risk of transmitting agents of animal spongiform encephalopathies. The procedure to follow and the documentation to be submitted are described in specific documents published by EDQM (Guideline on requirements for revision/renewal of certificates of suitability and Procedures for revision/renewal of certificates; see 7)

6.1.2 The dossier associated with the certificate will be updated after five years with at least a statement that no changes that may affect the quality, safety or efficacy of the substance have been made. After this renewal the certificate should normally be of unlimited validity provided the conditions for its validity, in particular those mentioned under 6.1.1, are respected.

6.1.3 In case where the monograph(s) to which the certificate refers is revised by the European Pharmacopoeia Commission, the manufacturer has to show compliance with the new requirements. The Certification Secretariat will ensure that the quality of the substance still meets the criteria of the revised monograph(s). The Secretariat will then either send a revised certificate to the holder or ask him to update its dossier in compliance with the revised monograph(s).

6.1.4 In case of new legal requirements or technical or scientific developments as regards health concerns, the Certification Secretariat ensures that the substance meets the new criteria. If not the certificate is suspended.

6.2 In case of failure to the above mentioned conditions or in case of major/critical deficiencies noticed during inspections, and based on the recommendation of the relevant board, the EDQM can suspend the certificate. The holder will be immediately notified by an official letter listing the reason of the decision and the conditions for restoring the certificate. The holder will be given the opportunity to present his position during an appropriate hearing with the relevant board. The licensing authority of the member states of the European

Pharmacopoeia Convention is immediately informed in confidence of the decision of the suspension.

7. REFERENCE DOCUMENTS

7.1 EU/EMEA documents:

- EC Directive on the Community code relating to medicinal products for human use (2004/27/EC) amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

- EC Directive on the Community code relating to medicinal products for veterinary use (2004/28/EC) amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

- CHMP/CVMP guideline on Summary of Requirements for Active Substances in the Quality part of the Dossier (CHMP/QWP/297/97; EMEA/CVMP/1069/02)

- The Rules governing medicinal products for Human and Veterinary use in the European Union :
  - Volume 4 Good Manufacturing Practice (Medicinal products for Human and Veterinary use)
  - Volume 2B Presentation and content of the dossier - (Medicinal products for Human Use)
  - Volume 6B Presentation and content of the dossier - (Veterinary medicinal products)

7.2 EDQM documents:

- Terms of Reference – PA/PH/CEP (01) 1

- Content of the dossier for chemical purity and microbiological quality – PA/PH/CEP (04) 1

- Content of the dossier for a substance for TSE risk assessment – PA/PH/CEP (06) 2

- Content of the dossier for herbal drugs and herbal drug preparations quality evaluation - PA/PH/CEP (02) 6

- Guideline on requirements for revision/renewal of certificates – PA/PH/CEP (04) 2

- Application form: request for new certificate of suitability – ECEP/03; request for revision or renewal of certificate of suitability - ECEP/05

- Procedure for management of revisions/renewals of certificates – PA/PH/Exp. CEP/T (04) 18