

COUNCIL OF EUROPE
PUBLIC HEALTH COMMITTEE
(Partial Agreement)

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.

1 INTRODUCTION

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

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

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

17 SCOPE

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

- 21 - organic or inorganic substances (active or excipients), manufactured or extracted.
- 22 - substances produced by fermentation as indirect gene products, which are metabolites of
23 microorganisms, irrespective of whether or not the microorganisms have been modified by
24 traditional procedures or r-DNA technology (see the monograph Products of Fermentation).
- 25 - products with risk of transmitting agents of animal spongiform encephalopathies (TSE) (see the
26 monograph Products with risk of transmitting agents of animal spongiform encephalopathies).

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

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

31 HOLDER OF THE CERTIFICATE

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

1 PROCEDURE

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

3 1. SUBMISSION OF THE DOSSIER

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

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

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

27 2. ACKNOWLEDGEMENT OF RECEIPT

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

33 3. DESIGNATION OF ASSESSORS

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

¹ HACCP = hazard analysis and critical control point.

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

- 2 - Report A or “Confidential report”. This report includes an exhaustive critical assessment of
3 the data provided and is kept in the confidential dossier for certification of suitability.
4 Report A can be made available, on request to any marketing authorisation body, in the
5 context of an identified medicinal product license application referring to this substance and
6 the manufacturer would be informed at the same time.
- 7 - Report B or “request for revision of the monograph”, when updating of the monograph is
8 requested, this report contains the information that the relevant Group of Experts of the
9 European Pharmacopoeia needs to update the monograph which has been shown to be
10 inadequate. It is prepared so as not to divulge the confidential information in the dossier.
11 This part of the report shall be sent to the manufacturer prior to its transmission to the expert
12 group concerned.
- 13 - Report C or “Comments for the inspectors”. This report contains any useful information for
14 an inspection and/or any specific request for inspection and specifies which GMP
15 guidelines/Quality Assurance system are referred to in the dossier when EU GMP
16 requirements do not apply.

17 4. ASSESSMENT

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

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

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

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

28 4.1 *The monograph is able to control the quality of the substance and/or the substance meets the*
29 *criteria of the monograph Products with risk of transmitting agents of animal spongiform*
30 *encephalopathies.*

31 Consequently, the certificate of suitability is granted.

32 As regards the chemical impurities, if necessary, the transparency of the monograph by
33 mentioning the impurity (ies) tested is improved while taking any measures required to
34 protect the confidentiality of the information (industrial property) with the agreement of the
35 manufacturer.

36 During a subsequent revision of the monograph, the names of known and controlled
37 impurities that do not concern matters of industrial property are published with the
38 agreement of the manufacturer. In the interim period this (these) impurity (ies) is (are)
39 mentioned in the certificate itself.

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

4
5 4.2 *The monograph is not able fully to control the quality of the substance, but the information*
6 *provided (new, validated, analytical method and/or additional tests) nevertheless guarantees*
7 *that the quality of the substance is adequately controlled (note: this situation is not*
8 *applicable for cases of TSE risk assessment).*

9 Consequently:

10 The certificate of suitability is granted. In the certificate is given the full text of the
11 additional test and the full list of named impurities including their limits controlled by that
12 test.

13 With the agreement of the manufacturer the Secretariat asks the relevant Group of Experts
14 of the European Pharmacopoeia to initiate the appropriate revision process to include an
15 adapted test so as to be fully suitable to control the quality of the substance from this
16 manufacturer as well.

17 If necessary, the transparency of the monograph by mentioning the impurity (ies) tested is
18 improved while taking any measures required to protect the confidentiality of the
19 information (industrial property) in agreement with the manufacturer.

20 During a subsequent revision of the monograph, the names of known and controlled
21 impurities that do not concern matters of industrial property are published in agreement with
22 the manufacturer. In the interim period this (these) impurity (ies) is (are) mentioned in the
23 certificate itself.

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

27
28 4.3 *The information supplied is incomplete and does not allow a conclusion.*

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

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

34
35 4.4 *The monograph is not suitable to control the quality of the substance and an agreement on*
36 *testing methods for (a) given impurity (ies) or an agreement on the TSE risk assessment has*
37 *not been reached or the information provided (even after several requests) do not*
38 *demonstrate compliance with the current requirements.*

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

8 5. NOTIFICATION OF THE DECISION

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

11 6. FOLLOW UP TO CERTIFICATION OF SUITABILITY

12 6.1 Failure to comply with the following will render the certificate void:

13 6.1.1 Any change (administrative or technical) that may or may not affect the quality, safety or
14 efficacy of the substance, must be reported to the Certification Secretariat of the EDQM so
15 that the dossier can be reassessed and updated.

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

22 6.1.2 The dossier associated with the certificate will be updated after five years with at least a
23 statement that no changes that may affect the quality, safety or efficacy of the substance
24 have been made. After this renewal the certificate should normally be of unlimited validity
25 provided the conditions for its validity, in particular those mentioned under 6.1.1, are
26 respected.

27 6.1.3 In case where the monograph(s) to which the certificate refers is revised by the European
28 Pharmacopoeia Commission, the manufacturer has to show compliance with the new
29 requirements. The Certification Secretariat will ensure that the quality of the substance still
30 meets the criteria of the revised monograph(s). The Secretariat will then either send a
31 revised certificate to the holder or ask him to update its dossier in compliance with the
32 revised monograph(s).

33 6.1.4 In case of new legal requirements or technical or scientific developments as regards health
34 concerns, the Certification Secretariat ensures that the substance meets the new criteria. If
35 not the certificate is suspended.

36 6.2 In case of failure to the above mentioned conditions or in case of major/critical deficiencies
37 noticed during inspections, and based on the recommendation of the relevant board, the
38 EDQM can suspend the certificate. The holder will be immediately notified by an official
39 letter listing the reason of the decision and the conditions for restoring the certificate. The
40 holder will be given the opportunity to present his position during an appropriate hearing
41 with the relevant board. The licensing authority of the member states of the European

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

3 7. REFERENCE DOCUMENTS

4 7.1 EU/EMA documents:

5 - EC Directive on the Community code relating to medicinal products for human use
6 (2004/27/EC) amending Directive 2001/83/EC on the Community code relating to medicinal
7 products for human use

8 - EC Directive on the Community code relating to medicinal products for veterinary use
9 (2004/28/EC) amending Directive 2001/82/EC on the Community code relating to
10 veterinary medicinal products

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

13 - The Rules governing medicinal products for Human and Veterinary use in the European
14 Union :

15 Volume 4 Good Manufacturing Practice (Medicinal products for Human and
16 Veterinary use)

17 Volume 2B Presentation and content of the dossier - (Medicinal products for
18 Human Use)

19 Volume 6B Presentation and content of the dossier - (Veterinary medicinal
20 products)

21 7.2 EDQM documents:

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

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

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

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

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

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

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