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# GUIDANCE DOCUMENT

Use of Certificates of Suitability as supporting information  
in Drug Submissions

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**Health Products and Food Branch**

Canada 

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*Également disponible en français sous le titre : Ligne directrice : Utilisation de certificats de conformité à titre d'information à l'appui des présentations de drogue*

## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

### Document Change Log

<b>Version</b>	Use of Certificates of Suitability as supporting information in Drug Submissions (2017)	<b>Replaces</b>	Use of Certificates of Suitability as supporting information in Drug Submissions (Jan 2017)
<b>Date</b>	August 21, 2017	<b>Date</b>	January 31, 2017
<b>Change</b>	August 21, 2017		
<b>Nature of and/or Reason for Change</b>	Guidance finalized  Changes in the content of this revision include updates as follows: <ol style="list-style-type: none"><li>1. Made changes requested during the January 2017 consultation. The consultation document is available on request.</li><li>2. Included information on use of micronised API.</li></ol>		

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## 1 INTRODUCTION

As required by Section C.08.002 of the *Food and Drug Regulations*, a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) must contain sufficient information and material to allow an assessment of the safety and effectiveness of the new drug.

The purpose of the guidance document is to outline the requirements when preparing submissions that rely on Certificates of Suitability (CEPs) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) to support the safety and effectiveness of a drug. This document is intended to provide guidance with regard to the Quality (i.e. [that is], Chemistry and Manufacturing) portion of submissions for drug substances that are filed with Health Canada pursuant to Division C.05 and C.08 of the *Food and Drug Regulations* and accompanied by a CEP.

Applicants (Drug Identification Number [DIN] owners or new applicants) now have the option to file a CEP in lieu of filing complete manufacturing information or the restricted portion of a type I Active Substance Master File (ASMF). The CEP can be provided in submissions filed pursuant to Division 5 and Division 8, Part C of the *Food and Drug Regulations*.

### 1.1 Policy Statements

#### 1.1.1 *Acceptance of Certificates of Suitability (CEPs)*

Health Canada reserves the right to determine the acceptability of an individual CEP. Health Canada does not envisage that a valid CEP will not be considered acceptable, however, going forward, factors not within Health Canada's control such as Ph.Eur. monographs for new types of products and the discretion of EDQM to change its requirements, means Health Canada needs to maintain some discretion to review complete Active Pharmaceutical Ingredient (API) Information. If a CEP is not considered supportive at any time in the life cycle of a drug product, Health Canada will request complete information from the API manufacturer to support the safety and efficacy of a drug product.

#### 1.1.2 *Active Pharmaceutical Ingredients (APIs) with the potential for biological contamination*

An ASMF is still required for APIs that have the potential of being contaminated with adventitious agents of human, animal or micro-organism origin (for example [e.g.] fermentation, sterile APIs). CEPs can be used to expedite the assessment process. In this case, the CEP can be filed in the ASMF in support of the suitability of the analytical methods to control the chemical quality of the API and to partially support a re-test period, if applicable (i.e., Health Canada will continue to assess microbial attributes for a

non-sterile API and the sterility for a sterile API). Health Canada will perform a detailed assessment of the manufacturing processes and controls as they relate to the microbiological quality.

### **1.1.3 Health Canada access to European Directorate for the Quality of Medicines (EDQM) documentation**

Health Canada reserves the right to access the EDQM assessment reports as necessary, subject to agreements with EDQM.

### **1.1.4 Good Manufacturing Practices (GMP)**

A CEP is not considered evidence of compliance with Canadian GMPs for APIs. CEPs certify that the chemical purity and microbiological quality of a manufacturer's drug substance is suitably controlled by the monographs of the European Pharmacopoeia. Consult the Health Canada website for information on GMPs for APIs.

## **1.2 Scope and Application**

This guidance document applies to New Drug Submission (NDS), Abbreviated New Drug Submission (ANDS), Clinical Trial Applications (CTAs) and all Veterinary Drug Submissions for drug substances of synthetic or semi-synthetic origin. This guidance document applies to new active pharmaceutical ingredients (APIs) and existing APIs. As such, the principles outlined below also apply to applications for drug identification numbers (DINAs) when a filing of an ASMF would have been otherwise considered necessary.

This guidance applies to APIs where a European Standard is elaborated in the European Pharmacopoeia (Ph. Eur.).

Drug substances which are not completely characterized as outlined in the guidance “Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)” are excluded from this guidance.

This guidance does not apply to Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs.

Transmissible Spongiform Encephalopathy (TSE) CEPs and Herbal CEPs are outside the scope of this guidance document.

For APIs prepared by microorganisms that are not subject to subsequent synthetic steps and not included in Schedule D (i.e., antibiotics), a full ASMF is still required. However, CEPs can be submitted in order to expedite the assessment process. The CEP can/should be filed in the ASMF

in support of the suitability of the analytical methods to control the chemical quality of the Active Pharmaceutical Ingredient (API). Semi-synthetic APIs are included in the scope of this guidance.

## **2 GUIDANCE FOR IMPLEMENTATION**

Applicants who wish to take advantage of this new filing option should submit the following data as part of their submission (CTA, NDS, ANDS or DIN A) or supplement to a new or abbreviated new drug submission (SNDS or SANDS).

For clinical trial applications, consult the appropriate CTA guidance.

For veterinary drug submissions, consult the applicable veterinary guidance documents for appropriate information to be submitted with a supporting CEP. At a minimum, the information submitted with a veterinary drug should include the minimum of the information in the veterinary guidance documents or that included in Section 2.2, whichever is less.

### **2.1 Cross referencing a Certificate of Suitability (CEP)**

A complete valid CEP including all annexes referenced in it and accompanying attestations from the API manufacturer as per section 2.1.1 should be filed in Module 1, Section 1.2.3. The Declaration of Access box in the CEP should be filled in by the certificate holder. When the API manufacturer and the CEP holder are not the same company, additional attestations may be necessary. Consult the Bureau of Pharmaceutical Sciences prior to submitting the CEP in this case (e.g., if the CEP is held by a broker).

#### ***2.1.1 Attestations from the API manufacturer to be submitted with the Certificate of Suitability (CEP)***

##### ***2.1.1.1 Authorisations regarding access***

The following written attestation should be provided:

1. The CEP should be accompanied by a written authorisation from the API manufacturer for Health Canada to refer to the CEP along with the EDQM assessment report and the specifications authorised by EDQM.
2. The API manufacturer should attest that they will provide Health Canada with a copy of the entire EDQM dossier and associated correspondence in electronic form on request from Health Canada.

### 2.1.1.2 Authorisations regarding the manufacture and testing of the Active Pharmaceutical Ingredients (APIs)

The following written attestation should be provided from the API manufacturer:

1. That GMP for APIs will be applied commencing with the introduction of the starting material authorised by the EDQM.
2. Written assurance that there have been no significant changes (i.e., no level 1 changes) in the manufacturing method and controls following the granting of the CEP, or its last revision.
3. That any conditions/additional tests attached to the CEP by the EDQM and any tests and limits additional to those in the Ph. Eur. monograph (for example, for particle size distribution, specific polymorphic form) required for the intended use of the substance will be applied to each batch of the drug substance destined for the Canadian market.
4. An attestation that any additional in-house methods identified in the API manufacturer's specifications are the ones submitted to the EDQM and the methods are used as described in the dossier submitted to the EDQM.
5. That the API that will be produced for the Canadian market will be manufactured in a manner using a manufacturing process that is identical to the route evaluated by the EDQM and that any in-process tests or tests of intermediates submitted to or requested by the EDQM will be applied in the manufacture of the API destined for the Canadian Market.
6. That the specifications provided to the applicant reflect the final API specifications submitted to and assessed by the EDQM.

The text of the attestations may be altered for accuracy with appropriate scientific justification and the provision of a side-by-side comparison of any differences in the dossier submitted to EDQM (e.g., due to additional tests on the API specifications required by an individual applicant). Only attestations that reflect equivalent or more rigorous practices will be accepted in conjunction with a CEP in a submission. If less rigorous practices are proposed, the CEP should be accompanied by an ASMF to allow for a complete assessment of the information. No change to the route of synthesis, including starting materials or intermediates and manufacturing controls will be accepted within this process. An ASMF would be required in this case to assess the differences.

For GMP requirements for APIs for Human and Veterinary Drugs, consult the Health Canada website.

## **2.2 Submitting information related to the Active Pharmaceutical Ingredients (APIs) in the Common Technical Document (CTD) Module 3**

The information equivalent to the information that would be provided in the Active Substance Master File (ASMF) “Applicant’s Part” should be obtained from the API manufacturer and supplemented by the applicant’s own data as necessary. This information should be current and should be provided in the appropriate CTD section of Module 3 rather than as a single block. Regardless of the information provided by the supplier of the drug substance, the manufacturer of the dosage form is responsible for ensuring that the quality of the drug substance is suitable for use in a drug product and meets the standard claimed throughout its re-test period. Only the CTD sections as listed below need to be included in Module 3. The API information in the Certified Product Information Document (CPID) should be provided in its entirety.

In a submission which references a valid CEP, the Quality Overall Summary (QOS) should be fully completed and Module 3 information should be submitted in the submission as follows:

### **2.2.1 Section S.2**

- a. Section S.2.1 should confirm that the API will only be sourced from the manufacturing site(s) listed on the CEP.
- b. A detailed chemical flow diagram should be included under section S.2.2 (a) to declare the starting material as accepted by the EDQM.
- c. Detailed information for sections S.2.2 to S.2.6 need not be submitted. If the API has been micronised to the specifications of the applicant, information on the micronisation of the API should be provided in the submission.

### **2.2.2 Section S.3**

- a. Data generated to support structure elucidation of the API need not be submitted.
- b. The maximum daily dose (MDD) and the route(s) of administration of an active substance approved in Europe are used as a basis to establish acceptable limits during evaluation of the CEP. If a new route of administration or a higher MDD than the known ones is declared by the applicant, the related information might need to be assessed accordingly. The applicant should identify any discrepancies between European and Canadian information on dosage and administration of the API and provide justification that the information used as the basis of acceptance of the limits in the CEP are valid for the Canadian dossier. This does not apply for Veterinary Drugs.
- c. All potential impurities in the API should be provided in a tabular form including a brief description of whether impurities are process related and/or degradants.

The information should be sufficient to complete the impurities section in the Certified Product Information Document (CPID) and the submission should declare impurities which are not routinely tested in the API but may need testing as a part of the justification for changes to the API manufacturing process.

### **2.2.3 Section S.4**

Analytical methods and their validation reports should also be provided if the drug product manufacturer's methods for testing the API are different from the methods authorised by EDQM (i.e., Ph. Eur. method or method appended to the CEP).

The API manufacturer's specifications should be provided along with the dosage form manufacturer's release specifications. The dosage form manufacturer should have drug substance specifications that are in agreement with the API manufacturer's specifications and the CEP. Applicants are strongly encouraged to adopt a Ph. Eur. standard for the drug substance to avoid the need to submit additional method validation data and increased assessment time. Any difference between these specifications from the release testing site and the specifications which the API manufacturer submitted to EDQM for assessment should be discussed and justified.

Results of batch analyses for two batches of the API should be submitted for new applications. For post approval applications the requirements listed in the Post NOC Guidance should be followed. These batches should include the lot(s) of API used in the pivotal drug product lots (e.g., those lots used for bioequivalence studies or 2 lots used for Phase III clinical trials).

Should a different standard be claimed, the applicant is advised that the specifications would need to include a test for additional impurities as reported on the CEP and discuss the ability of the proposed analytical methods to adequately control the impurities identified on the Ph. Eur. monograph transparency list if the impurities are relevant to the synthetic route when these impurities are not specified by the proposed standard.

### **2.2.4 Section S.6**

- a. No documentation to support the CCS is necessary unless no re-test period and packaging is indicated on the CEP.

### 2.2.5 Section S.7

- a. Stability data need not be filed to support the declared retest period if the proposed storage conditions and re-test period claimed by the applicant is the same as the one mentioned on the CEP. If the API has been micronised to the specifications of the applicant, stability data for the micronised API should be provided in the submission or justification provided that the stability data used to support the retest period on the CEP are applicable to the micronised API.
- b. Storage conditions for a drug substance imported into Canada should be declared according to the guidance document *Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*.

### 2.3 Cases where a Certificate of Suitability (CEP) is provided in partial support of the submission.

In all cases mentioned below, an ASMF should be provided, however the CEP can be provided in partial support of the submission and to expedite the assessment process.

- a. For a sterile API, complete information on the sterilization processes used for the API and the container closure system as well as complete results of their validation should be provided in the submission to Health Canada and the CEP can be used to support the steps prior to the sterilization steps.
- b. In cases where the API does not have a CEP, a CEP can be used to support a starting material when a Pharm. Eur. monograph exists for this material and subsequent transformations are fully described in the Active Substance Master File (ASMF).
- c. A CEP can be filed in an ASMF for similar forms of the same API (e.g., hydrates vs. anhydrate) to support aspects of the manufacturing and/or testing of the API. A side-by-side comparison table of the information filed in the EDQM dossier for the CEP and the information filed for the form represented in the ASMF should be provided in Section 1.0.7 General Note to Reviewer.
- d. A CEP can be filed in partial support of a drug substance standard other than the Ph.Eur. standard. For example, if a United States Pharmacopeia (USP) standard is declared, then supporting documentation submitted should include equivalency of methods with the USP standard. The specifications (including the related substance method) used to control the drug substance should be the same specifications and method as submitted to the EDQM. If USP methods are not used in addition to the methods used to claim a Ph.Eur. standard for USP specific impurities (i.e., if a house method is used or the Ph.Eur.

method used differs from the USP method), the suitability of the specification to show conformance to the USP standard should be addressed.

## **2.4 Managing the Certificate of Suitability (CEP) Lifecycle**

### **2.4.1 Post Notice of Compliance Changes**

When a CEP has been used to support authorisation of a drug for the Canadian market, it is expected that the CEP will remain valid throughout the life of the drug product. Changes to the status of the CEP should be notified immediately to the customer using the API for the Canadian market. Withdrawal of a CEP by the EDQM or the owner, suspension or cancellation of a CEP should be followed by appropriate action on the DIN owner's part as the source of API may no longer be considered acceptable by Health Canada.

The holder of a Certificate of Suitability is responsible for maintaining the certification dossier and informing their customers of any changes to the CEP and the nature of those changes. The API manufacturer should provide their customers with the revised CEP and revised Module 3 information when it would involve changes to the information which would be considered the equivalent of information that would be submitted in the Applicant's part of an ASMF. The DIN owner is responsible for using API of suitable quality in their drug product and should ensure sufficient manufacturing details have been provided to the drug product manufacturer to allow the drug product manufacturer to evaluate the impact of the changes on the API quality controls and the drug product quality.

An appropriate regulatory filing should be submitted by the DIN owner to Health Canada as necessary and in accordance with the guidance *Post-Notice of Compliance (NOC) Changes: Quality Document* or with the Guidance Document: *Post-Drug Identification Number (DIN Changes)*. The revised CEP and the accompanying attestations should be used to support subsequent regulatory filings for drug products which use this source of API.

Examples of this may include:

- a. A CEP may be re-issued because the EP monograph has been updated. This is considered an annual notification as the DIN owner is required to comply with C.01.004 and update their specifications accordingly.
- b. When as a result of a change in a manufacturing process, a new impurity needs to be controlled; the impact on the API specifications should be assessed. The dosage form manufacturer should determine the need to revalidate their analytical method for the new impurity and revise specifications to control it as an

unidentified impurity or specify the impurity. An annual notification can be submitted, provided that the manufacturing process change is also considered an annual notification.

#### **2.4.2 Suspension and Withdrawal of Certificates of Suitability (CEPs)**

A drug product which is manufactured from an API where the CEP has been provided in partial or complete support of the suitability of the API and the CEP has been subsequently suspended or withdrawn may not be marketed in Canada.

At the time a CEP is suspended or withdrawn, the DIN owner should take the appropriate corrective action, including notifying the Health Product Compliance Directorate if necessary. If necessary, appropriate corrective action should be taken, such as: conducting recalls of any affected lots in accordance with recall procedures, developing an action plan to avoid a product shortage situation and filing a drug submission with appropriate manufacturing changes to effectively address the potential safety concerns.

When a CEP is suspended due to GMP issues, Health Canada retains the authority to decide on the appropriate action related to the marketing of the product. After a CEP is re-instated by EDQM, marketing of the product may not commence until Health Canada has given the DIN owner of the drug product authorisation to market the product in accordance with Health Canada procedures.

### **3 REFERENCES**

1. Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)
2. Master Files (MFs) - Procedures and Administrative requirements (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mf-guide-ld-fm-eng.php>)
3. Certified Product Information Document- Chemical Entities (CPID-CE) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/templates/certified-product-information-document-chemical-entities-cpid-applications-submissions-drug-products.html>)
4. Post-Notice of Compliance(NOC) Changes: Quality Document (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html>)

5. Post-Drug Identification Number (DIN) Changes  
(<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-drug-identification-number-changes.html>)
6. Glossary of Quality Terms
7. International Generic Drug Regulators Program ASMF/DMF Lexicon of Quality Terms  
([https://www.igdrp.com/sites/default/files/IGDRP%20ASMF\\_DMF%20WG%20Lexicon%20of%20Quality%20Terms.pdf](https://www.igdrp.com/sites/default/files/IGDRP%20ASMF_DMF%20WG%20Lexicon%20of%20Quality%20Terms.pdf))
8. Guidance for Industry - Preparation of Veterinary NDSs  
(<https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/legislation-guidelines/guidance-documents/guidance-industry-preparation-veterinary-new-drug-submissions-health-canada-2007.html>)
9. Guidance for Industry - Preparation of Veterinary ANDSs - Generic Drugs  
(<https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/legislation-guidelines/guidance-documents/guidance-industry-preparation-veterinary-abbreviated-new-drug-submissions-generic-drugs-health-canada-2009-1.html>)

## **APPENDIX A - TEMPLATES FOR ATTESTATIONS FROM THE ACTIVE PHARMACEUTICAL INGREDIENTS (APIS) MANUFACTURER**

On behalf of [API Manufacturer Name], I attest to the following:

1. I authorise Health Canada to refer to the CEP along with the EDQM Assessment report and the specifications authorised by EDQM.
2. I attest that [API Manufacturer Name] will provide Health Canada with a copy of the entire EDQM dossier and associated correspondence in electronic form on request from Health Canada.
3. I attest that GMP for APIs will be applied commencing with the introduction of the starting material authorised by EDQM.
4. I attest that there have been no significant changes (i.e., no level 1 changes) in the manufacturing method and controls following the granting of the CEP, or its last revision, by EDQM.
5. I attest that any conditions/additional tests attached to the CEP by the EDQM and any tests and limits additional to those in the Ph. Eur. monograph required for the intended use of the substance will be applied to each batch of the drug substance destined for the Canadian market.
6. I attest that the in-house method [insert reference to in-house method(s) not mentioned on the CEP has/have] been submitted to the EDQM and are used as described in the dossier submitted to EDQM.
7. I attest that the API that will be produced for the Canadian market will be manufactured in a manner using a manufacturing process that is identical to the route evaluated by the EDQM and that any in-process tests or tests of intermediates submitted to or requested by EDQM will be applied in the manufacture of the API destined for the Canadian Market.
8. I attest that the specifications provided to the applicant reflect the final set of API specifications and the in-house method(s) listed on the specifications which were submitted to and assessed by the EDQM.

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Signed by [Authorised representative name]  
[Position title]  
[API Manufacturer Name]