Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

Use of Certificates of Suitability as supporting information in Drug Submissions

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Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

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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.

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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.

Sponsors now have the option to file a CEP in submissions filed pursuant to Division 5 and Division 8, Part C of the *Food and Drug Regulations* in lieu of filing complete manufacturing information or a type I Active Substance Master File (ASMF).

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. 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 Active Pharmaceutical Ingredients (APIs) 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. 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. Health Canada will perform a detailed assessment of the manufacturing processes and controls as they relates 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 review 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.

1.2 Scope and Application

This guidance document applies to New Drug Submission (NDS), Abbreviated New Drug Submission (ANDS), Clinical Trial Applications (CTAs) and 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 number submissions (DINAs) when the filing of a MF would have been otherwise considered necessary.

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

Drug substances which are not completely characterized are excluded from this guidance.

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

For drugs prepared by microorganisms but not included in Schedule D (i.e., antibiotics), a full MF is still required. CEPs can, however, be used 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).

2 GUIDANCE FOR IMPLEMENTATION

Sponsors who wish to take advantage of this new filing option should submit the following data as part of their supplement to an abbreviated new drug submission (SANDS):

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 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 BPS prior to submitting the CEP 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 Report A 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 starting material authorised by EDQM.
2. Written assurance that there have been no significant changes in the manufacturing method and controls following the granting of the CEP, or its last revision, by EDQM.
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 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 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 EDQM.

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

The Drug Master File (DMF) "Applicant's Part" should be obtained from the API manufacturer and supplemented by the sponsor'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, Module 3 information should be submitted in the SANDS 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.

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 reviewed 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.
c. All potential impurities in the API should be provided in a tabular form including a brief mention 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 declare impurities which are not routinely tested but may need testing as a result of change controls.

2.2.3 Section S.4

Analytical methods and their validation reports should also be provided if the methods used 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. Sponsors 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 review time.

Specifications for the drug substance from the release testing site for the API should be submitted. Any difference between these specifications 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. 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 Container Closure System (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 if the proposed storage conditions and re-test period claimed by the sponsor is the same as the one mentioned on the CEP.

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 and the CEP can be used to support the steps prior to the sterilization steps.

b. 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. The specifications including the related substance method used to control the drug substance should be the same specifications and method as submitted to EDQM. If USP methods are not used in addition to the methods used to claim a Ph.Eur. standard for USP specific impurities, the suitability of the specification to show conformance to the USP standard should be addressed.

2.3 Managing the Certificate of Suitability (CEP) Lifecycle

2.3.1 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 dossier affecting the quality of the API. 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.

An appropriate regulatory filing should be submitted by the DIN owner to Health Canada as necessary and in accordance with the Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document. 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 the manufacturing process change is also considered an annual notification.

2.3.2 Closure, Suspension and Withdrawal of Certificates of Suitability (CEPs)

A product which is manufactured from a drug substance where the CEP has been suspended or withdrawn may not be marketed in Canada.

At the time a CEP is closed, suspended or withdrawn, the DIN owner should notify the Health Product Compliance Directorate immediately. 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 manufacturing site for the drug substance authorisation to market the product in accordance with Health Canada procedures.

3 REFERENCES

1. Guidance Document: Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

2. Draft Guidance Document: Master Files (MFs) - Procedures and Administrative requirements

3. Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document

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 Report A 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 starting material authorised by EDQM.

4. I attest that there have been no significant 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.

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