

Use of CEPs within the Canadian Regulatory Framework.

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Health Canada's experience with CEPs

- How we currently use CEPs
- Our history - how we adopted CEPs
- Recently published guidance
- Current developments

CEP use in Canada

- Process from 2007 to today - Use of CEP in conjunction with an ASMF
 - ASMF submitted but not assessed
 - From 2012, ASMF can be assessed if differences are proposed from what has been submitted to EDQM (minimal assessment performed and only to assess the differences)
- Process from August 21, 2017
 - CEPs can now be submitted in lieu of an ASMF
 - Minimal API information required in Module 3
 - Drug product manufacturers specifications and analytical methodology assessed as necessary (e.g., different analytical methods, testing relevant to the proposed dosage form such as particle size distribution, polymorphs)
 - Retest period assessed if not covered by CEP or the applicant proposes a re-test period that is longer than that listed on the CEP
 - If detailed information is provided on the API in Module 3 it is not assessed

Confidence Building exercise

- Process occurred over several years starting in 2004
- Overall findings - the EDQM evaluation process is similar to that done by Canadian assessors and the confidence building exercise confirmed that the evaluation is considered equivalent
- Findings based on:
 - Initial visit to EDQM (2004) to study assessment process, example files, SOPs
 - Involvement in the assessment of API dossiers during evaluation sessions
 - Pilot program between 2007 and 2017 where CEPs were accepted along with an ASMF. Initially the MF could still be assessed, but it rapidly became clear that the MF need not be assessed.
 - EDQM guidelines for assessment indicate that the scope and rigour of the assessment is equivalent to the assessment that would have been performed by Canadian assessors
- Legal opinion on acceptance

Benefits of the appointment of EDQM assessors

- Appointment of Canadian assessors as EDQM assessors allows for ready availability of guidance and assessment reports
- Interaction between other European assessors led to better harmonization of activities and guidance
- Better understanding of how the CEP process fits in with European processes allowed us to solve issues more easily
 - Examples – differences in the labelling of storage conditions in the EU and in Canada
- Adopt processes that meet the Canadian regulations/guidance

Canadian regulations for pre-market authorisation

- Legal opinion sought
- Health Canada (i.e. “the minister”) determines the acceptability of a CEP to support a submission
- Manufacturer’s standards - C.01.011 (4) of the Canadian Food and Drug Regulations

No person shall use a manufacturer’s standard for a drug that provides

 - (a) a lesser degree of purity than the highest degree of purity, or
 - (b) a greater variation in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the Act.

Schedule B lists compendia that are official in Canada

- USP, Ph.Eur, International Pharmacopoeia

Health Canada Guidance Document

- **Title: Use of Certificates of Suitability as supporting information in Drug Submissions**
- Applicants now have the option to file a CEP in lieu of having an ASMF filed with Health Canada
- Provides details and guidance for managing the CEP lifecycle (e.g., regulatory filing procedures for post-approval changes, actions for suspensions/withdrawals of CEPs)
 - Consultation on the guidance January – May 2017
 - Published and implemented on the 21st August 2017
 - No significant experience to date with the guidance due to it's recent publication
 - Expected that the guidance will be updated if necessary on a 2 year schedule

Why do we ask for Attestations?

- Based on experience with the confidence building exercise
- Found that manufacturers were not providing ASMFs with identical data to that seen on the CEPs.
- Examples
 - USP standard declared and testing to the USP monograph proposed
 - Additional purification steps
 - Different batch sizes
 - Different declaration of the starting material
- Easily dealt with when we have a MF and data to assess, but not appropriate when no data/ASMF being provided.

Attestations from the API manufacturer

- 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.
- I attest that GMP for APIs will be applied commencing with the introduction of the starting material authorised by EDQM.
- 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.
- 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.

Attestations, cont.....

- 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.
- 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.
- 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.

Data requested is NOT FOR ASSESSMENT

- Except where no retest period is on the CEP, the data requested to accompany the CEP is not requested for assessment.

2.2.1 Section S.2

- Section S.2.1 should confirm that the API will only be sourced from the manufacturing site(s) listed on the CEP.
- A detailed chemical flow diagram should be included under section S.2.2 (a) to declare the starting material as accepted by the EDQM.

2.2.2 Section S.3

- 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.

Ph.Eur. Standards vs USP standards

- Many products on the Canadian market are also produced for the US market
- Since both the Ph.Eur. And the USP are official compendia in Canada, we find that declaration of standards is roughly split between Ph.Eur. and USP
- When a CEP is available, many drug product manufacturers want to claim USP standards
- Pilot process allowed us to develop methods and guidance to allow for declaration of a USP standard but still allowing the CEP use
 - Process mainly involves assessment of equivalence of USP and Ph.Eur. methods
 - Not ideal – our preference is that the Ph.Eur. standard is declared, but efficiencies gained from acceptance of the CEP are greater than the work necessary to confirm that the testing and declaration of a USP standard is appropriate

Text from guidance re standards

- 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.

Results of the consultation on the guidance

- Some applicants find the process overly onerous
- Examples
 - Having to provide the attestations and limited API information in Module 3.
 - Applicants want more flexibility to make changes within the Annual Notification category of as per Canadian guidance for post-Notice of Compliance Changes
- Otherwise consultation comments were to request clarity on the scope of what is acceptable and what differences are allowed between EDQM accepted specifications/method of manufacture and Canadian proposed specifications while remaining within the scope of the framework.

CEPs provided in partial support of the submission

- Same process as previously - an ASMF should be provided, however the CEP can be provided in partial support of the submission and to expedite the assessment process.
 - 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.
 - 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).
 - 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.

Use of foreign reviews in Canada

- Two broad frameworks for acceptance of Foreign review reports:
 1. The CEP framework, where the certificate is accepted and assessment is administrative.
 2. Use of a copy of the foreign review report as part of the assessment procedure
- Assessors report that there are few efficiencies gained with using foreign review reports
- The CEP framework is found to be efficient, and time savings are significant in comparison to either a complete assessment or to using a foreign report

Next steps

- CEPs have been accepted since 2007. The scope of this acceptance was limited to TSE certifications, and CEPs for synthetic and semi-synthetic APIs.
- CEPs for Sterile APIs and fermentation products have not been accepted to date. The proposal is to expand the scope of acceptance of CEPs to include sterile APIs and fermentation products.
- BPS will accept CEPs for sterile APIs or APIs produced by fermentation with an ASMFs to complete confidence building exercise.
- This would subsequently allow for inclusion of these CEPs in the scope of the CEP Guidance document during the biannual updates to the guidance.
- As we gain knowledge and work within the framework of the new guidance, if there are opportunities for a less onerous process while still ensuring that it meets Canadian regulatory requirements, changes will be considered.

Gaining efficiency and reducing the red-tape burden

- The Abbreviated New Drug Submission team recently underwent an evaluation of the process using Lean methodology
- Looking for new ways to streamline the assessment process so that time to market authorization is reduced
- Regulatory Review of Drugs and Devices – a ministerial priority for the Canadian government
- As we gain knowledge and work within the framework of the new guidance, if there are opportunities for a less onerous process while still ensuring that it meets Canadian regulatory requirements, changes will be considered.

Questions?

- Questions on chemistry and manufacturing issues can be directed to the email address:

bps_enquiries@hc-sc.gc.ca

- Administrative questions on ASMFs can be directed to:

dmf_enquiries@hc-sc.gc.ca

Links to Canadian guidance documents

- Use of Certificates of Suitability as supporting information in Drug Submissions

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-use-certificates-suitability-supporting-information-drug-submissions.html#appa>

- Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions and Abbreviated New Drug Submissions

Will be published shortly on the Government of Canada website