

Certification of Substances Department

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Certification of suitability to the Monographs of the European Pharmacopoeia

CEP holders responsibilities towards their customers

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1. Introduction

In the recent years and in particular during the issue related to nitrosamine contamination of drug substances (and drug products), the EDQM as well as its international partners have noticed that Certificates of Suitability (CEP) Holders may often lack knowledge and awareness regarding the extent of their various responsibilities towards their customers.

These customers are the marketing authorisation applicants/marketing authorisation holders/sponsors, (the acronym MAH is used for all scenarios) that use their CEP(s) in the regulatory filing at the time of the application but more importantly during the post-authorisation phase, i.e. during the lifecycle of a medicine.

In order to overcome the obstacles mentioned-above, the EDQM has decided to provide clarity regarding the extent of the core responsibilities of CEP holders.

2. Requirements of CEP procedure and regulatory framework

Core responsibilities are specified in the commitments requested from CEP holders/applicants at the time of submission of a CEP application or CEP variation.

As applicable, and in addition to GMP requirements of ICH Q7/EU GMP Part II (section 17), those responsibilities are supported by the requirements laid down in various regulatory frameworks in Europe and beyond, such as

- EU Directive 2001/83/EC (M2, 32. (7))
- TGA's Guidance 11: Drug Master Files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for drug substances section 11.7.

CEP holders, as part of the medicines licensing systems, therefore have similar obligations to MAH with respect to the manufacturing activities (but related to the APIs) and information described in part 3.2.S of the Common Technical Document.

It should be noted that given the complex supply chain in a globalised world, some CEP holder's responsibilities might be delegated, but the overall responsibility with regard to the accuracy of the information laid down in the CEP dossier lies with the CEP holder.

CEP holders shall also provide sufficient information towards MAHs in order to enable them to fulfil their respective legal responsibilities.

Last but not least CEP holders are advised that as part of the scope of GMP inspections organised and conducted by EDQM it is verified whether CEP holder responsibilities are being taken into account, regardless of which stage of the manufacture/supply chain of an API is being inspected, and this aspect will be reinforced.

3. Responsibilities

The following are a list of the identified responsibilities of the CEP holder to the MAH;

- a. Provide the MAH with the most recent version of the CEP in a timely manner
- b. Sharing of pivotal information which is not on the CEP document or its annexes

In addition to the CEP itself, CEP holders should provide the MAH with *any necessary information that is needed to guarantee the quality, safety and efficacy of the medicines* e.g. information on the route of synthesis of the API, details of risk evaluations for impurities that CEP holders have performed (nitrosamines, elemental impurities, etc.).

- c. Variations / CEP revisions

To allow the MAH to evaluate the impact of any change introduced by the API manufacturer/CEP holder, regardless of whether it leads to a revision of the CEP and to update the marketing authorisation information, it is of utmost importance that the CEP holder provides the necessary information to their customers. Depending on the criticality of the change, the quality agreements in place should specify whether the implementation needs pre-approval by the MAH.

- d. Transparency in case of failures in fulfilment of the Certification procedure requirements, quality issues (e.g. nitrosamine) and/or serious GMP non-compliance of manufacturing sites involved

CEP holders are expected to notify without delay their customers/MAHs in cases where their CEP has been either suspended, withdrawn or expired, together with the reasons for such actions. Such changes to the status of a CEP have an impact on marketing authorisation applications and require immediate actions by the MAH.

- e. Data integrity

CEP holders should assure that all data relating to the process development, regulatory filing, GMP activities, including relevant marketing authorisation variations, are reliable, complete and accurate.

- f. Outsourcing/technical agreements if the CEP holder is different from the API manufacturer(s)

If an outsourced activity is one that may affect compliance with the CEP dossier (typical outsourced GMP activities are the manufacture of intermediates, partial or full testing of API, recovery of solvents etc.), there should be controls in place that provide assurance that the requirements of the CEP procedure are complied with. This also has relevance in relation to activities concerning post-approval changes and their implementation. A typical tool to establish the relation between the parties is a technical quality agreement specifying respective responsibilities and communication processes relating to the outsourced activities. All arrangements for outsourced activities must be in accordance with regulations in force and the CEP dossier for the product concerned and agreed by both parties.

4. References:

- [ICH Q7](#)
- [CHMP Opinion for the Article 5\(3\) of Regulation \(EC\) No 726/2004 referral on nitrosamine impurities in human medicinal products; Q&A no. 16](#)
- [CEP Procedure, Application form: All Holder's Commitments](#)
- [ICH Q12 section 6.2 change management across supply chain and product lifecycle](#)
- [Compilation of Union Procedures: "Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health".](#)
- [TGA's Guidance 11: Drug Master Files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for drug substances section 11.7](#)