

# THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



# Indian Pharmaceutical Alliance - 8<sup>th</sup> Global Pharmaceutical Quality Summit 2023

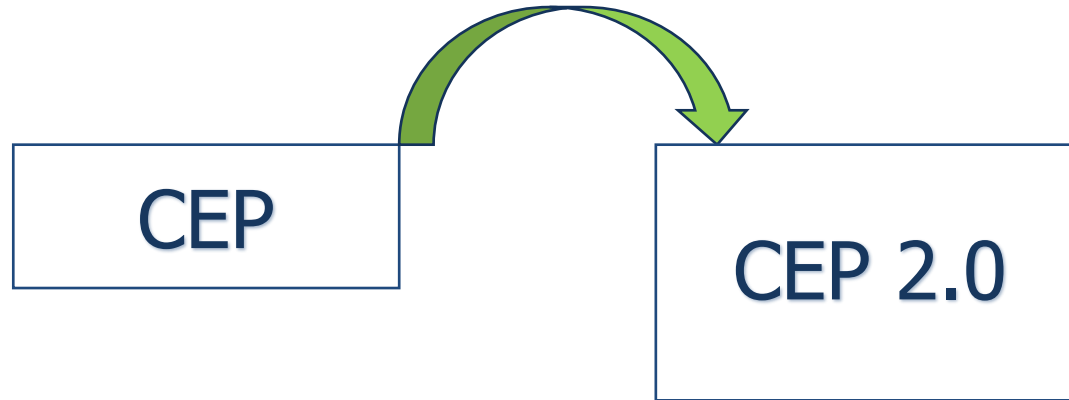
## **Session 12: CEP 2.0 – CEP of the Future**

Dr Thomas Hecker, GMP Inspector,  
EDQM Certification of Substances Department

23<sup>rd</sup> June 2023

# Why CEP 2.0?

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## **“new-look” CEP:**

- ✓ **meets the current needs of stakeholders**
- ✓ **offers greater transparency**
- ✓ **reduces the regulatory burden**

# What will change



Area 1: CEPs and information reported



Area 2: Changes regarding assessment of CEP applications



Area 3: On-line public certification database



Area 4: Authorities Database



Area 5: Fostering information sharing between CEP holders & MAH



Area 6: Reduction of revisions of CEPs



Area 7: Impact of changes and their implementation



Area 8: Trainings for assessors, CEP holders and CEP users



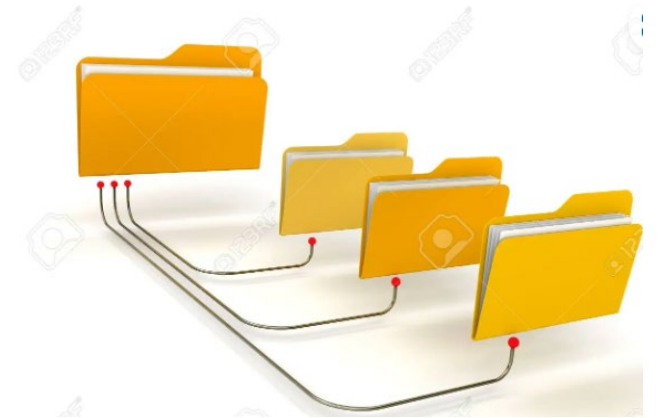
Area 9: Revising documents available on the website



Download the [document](#) explaining the implementation

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# Requirements to the dossier: content and structure



# The CEP 2.0 – requirements to the dossier

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## Application form and Module 1

- updated application forms in force as of 1 June 2023 (available on the EDQM website [link to application forms](#))
  - Holder's Commitment updated to reflect the CEP holder's responsibilities towards their customers and to anticipate potential confidential sharing of reports for the dossier with Competent Authorities of those countries with which the EDQM has a Memorandum of Understanding and/or Confidentiality Agreement in place.

# The CEP 2.0 – requirements to the dossier

## What has changed:

- **SPOR:** Organisation (Org) and Location (Loc) ID becomes mandatory for all sites listed in the application form. Org and Loc ID will be reflected on the CEP

**ACTION:** include EMA OMS

SPOR Org ID and Loc ID in the application form for all sites

<https://spor.ema.europa.eu/omswi>

**Instructions:**

<https://spor.ema.europa.eu/omswi/#/viewDocuments>

The screenshot displays the SPOR - Organisations Management System interface. At the top, there is a navigation bar with tabs for 'Substances', 'Products', and 'Organisations'. Below this, there are links for 'SPOR Home', 'Organisations', and 'Documents'. The main content area shows the 'View Organisation Location' page for a specific organisation. The 'Organisation Details' section includes the following information:

Organisation ID:	ORG-100003964
Organisation Name:	European Directorate For The Quality Of Medicines And Healthcare
Acronym:	EDQM
Status:	ACTIVE
Organisation Type:	Regulatory Authority EU Institution/Body/Agency

The 'Location Details' section includes the following information:

Location ID:	LOC-100000120
Address:	EN 7 Allee Kastner Cs 30026 Strasbourg Cedex 67081 France

# The CEP 2.0 – requirements to the dossier

## Reminder on the importance of comparative table in applications for revisions



**Changes must be individually classified and declared in the comparative table**

**IF NOT, change(s) considered as: not declared = not assessed = **not approved****



### 3. Comparative table

The comparative table should highlight the differences between the approved and proposed text of module 3, together with the correct classification of each change according to the EDQM Guideline for revisions. The justification for the changes should be fully developed in the cover letter.

Annexes	Yes	N/A
7) Comparative table	<input checked="" type="checkbox"/>	

[link to the refresher on good practices](#)



# The CEP 2.0 – requirements to the dossier

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CEP dossier (modules 2 and 3) will reflect the assessment performed and the approved specification

The process description and the specification sections of the CEP dossier should contain **only the information** corresponding to the **quality claimed**

Any other data **should not be** included in the dossier if **no corresponding** specific **grade** is requested

**ACTION:** include only relevant information in the dossier

# The CEP 2.0 – requirements to the dossier

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## **Maximum Daily Dose (MDD):**

- The CEP holder/applicant is requested to include in their dossier (in 3.2.S.1.3) the Maximum Daily Dose (MDD), route of administration and treatment duration considered for the development of their control strategy and specification presented in their CEP dossier.
- This information is also to be shared between the CEP holder and the drug product manufacturer/MAH.

# The CEP 2.0 – requirements to the dossier

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## **GRADES: Optional (no change), but:**

- In all cases, all sections of the dossier should be consistent within the dossier itself **and** with the CEP when granted
- If the applicant **does not apply** for a grade, data on micronisation, particle size, sterilisation, etc. should not be included in the dossier.
- Only if a grade is claimed, sites in charge of the concerned physico-chemical treatments such as milling, micronisation and sterilisation should also be listed in 3.2.S.2.1.
- If a grade is not requested, the information for the related sites should not be included in the CEP dossier and application.

# The CEP 2.0 – requirements to the dossier

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## QUALITY OF WATER:

- Section **3.2.S.2.3** should specify the quality of the water used within the manufacturing process.
- Choice and definition of water quality should be based on the EMA “Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)” and Ph. Eur.
- More information about the quality of water may be required at the level of the marketing authorisation application with regard to the intended final use of the substance.

# The CEP 2.0 – requirements to the dossier

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**Approved specification** (as in the section 3.2.S.4.1) will be appended to the CEP;

- the specification sections of the CEP dossier should contain only the information corresponding to the quality claimed
- Specification for micronisation, particle size, microbiological controls, etc. should not be included in the dossier if no corresponding specific grade is requested.
- Any **additional methods** needed to control the quality of the substance included in the specification will be assessed (validation, cross-validation) and appended to the CEP

# The CEP 2.0 – requirements to the dossier

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## **Expectations to the specification included in module 3:**

- should be free of highlighting, tracked changes, coloured text, and watermarks. The given text should be legible and the use of scanned documents is to be avoided.
- All headers and footers will be removed by EDQM during preparation of the Annexes and CEP holders/applicants are encouraged to avoid their use in sections 3.2.S.4.1 and 3.2.S.4.2 of their submissions.
- The tabular format is requested. Parameters, limits and reference of the method to be reported in the table (e.g. Ph. Eur., in-house).
- In case of in-house impurities controlled in the final substance, an unequivocal chemical name of the compound should be used (in-house code may be added if relevant).

# The CEP 2.0 – requirements to the dossier

## Example of the specification:

Parameters	Limits	Reference
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.	Ph. Eur. current edition
Identification Test A (IR) Test B (HPLC)	Complies to reference Positive	Ph. Eur. current edition
Specific optical rotation (o.d.b.)	+158° to + 167°	Ph. Eur. current edition
Loss on drying	≤ 0.5 %	Ph. Eur. current edition
Related substances		Ph. Eur. current edition
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Impurity C	≤ 0.15%	
Impurity D	≤ 0.15%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.5%	
Assay (o.d.b.)	97.0% to 102.0 %	Ph. Eur. current edition
Residual solvents (by GC)		In-house
Ethanol	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house

# The CEP 2.0 – requirements to the dossier

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## Analytical Methods

- Details of the methods of the Ph. Eur. monograph **should not** be reproduced in section 3.2.S.4.2. This applies also in case chromatographic adjustments are made to the Ph. Eur. method within the scope of Ph. Eur. chapter 2.2.46.
- Subsection 1 –Alternative analytical test procedures (validated and determined to be equivalent) to those of the Ph. Eur. monograph
- Subsection 2 – Additional in house test procedure(s) (validated) are those necessary to ensure the quality of the substance when the Ph. Eur. Method(s) is not suitable to control in-house impurities and/or to supplement monograph methods.



# The CEP 2.0 – requirements to the dossier

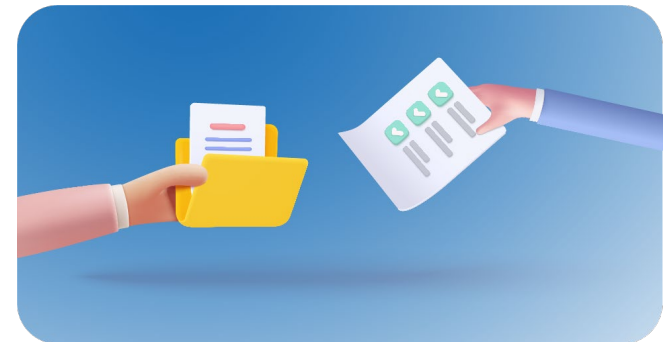
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## Stability

- Encouragement to include stability data in CEP applications and to claim re-test period to benefit from the centralised assessment of these data at the level of the CEP
- More flexibility with regard to storage conditions / temperature
  - Restrictive storage conditions with respect to temperature may be accepted and reflected on the CEP with the re-test period, provided they correspond to the conditions in which stability data have been obtained.
- Assessment of stability data with reference to additional climatic zones (III and IV) and inclusion of corresponding re-test period on CEPs if proposed by applicants (optional).

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# Fostering information sharing



# Fostering information sharing CEP holders & MAH

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- CEP holder shall provide information to their customers in addition to the CEP. CEP holder and MAH agree on information shared and format.
- In January 2022 the document “CEP holders responsibilities towards their customers” was published as a reminder to CEP holders (EDQM web-site)
- This aspect is checked during EDQM GMP inspections.
- Reinforcement of this responsibility in 2023
  - A commitment as part of the application form for a CEP
  - A specific sentence on this obligation will be reported on the CEP document
  - Publication of history of procedures in the public certification database, so users are aware of changes and can ask details from the CEP holders.

# Fostering information sharing CEP holders & MAH

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No declaration of access box in the CEP document anymore: replaced by a 'Letter of Access' – template letter will be available on the EDQM website.

## **ACTION:**

**Holders should provide their customers with the letter of access and can use the template available on the EDQM website**

Note: If regulatory authorities outside Europe have a template letter, it is recommended to use that one.

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# Reduction of revisions of CEPs



# Reduction of revisions of CEPs

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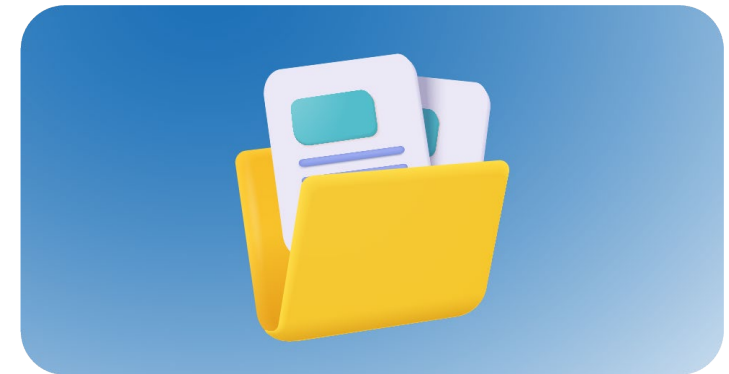
- CEPs no longer revised for changes not impacting their content even in case of major revisions.
- Stop releasing a “renewed” CEP following the renewal procedure (the renewal process will be kept), except if the content is impacted

→ impact on the CEP numbering

- This will concern CEPs already in the “new look”.

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# On-line public certification database



# On-line **Public** Certification database

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## New features in addition to current ones

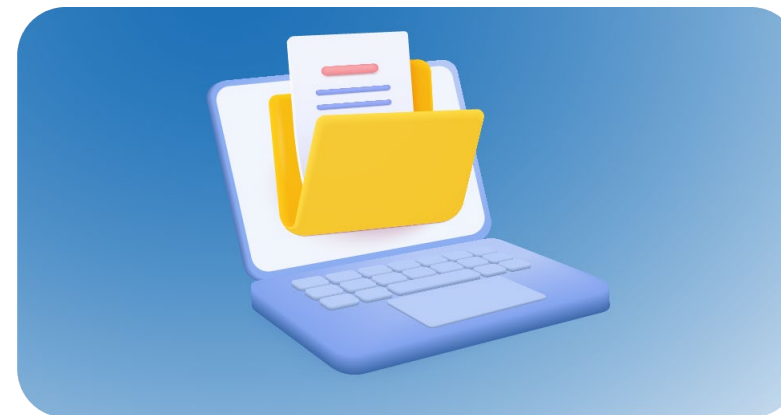
- EMA SPOR OMS ORG\_ID and LOC\_ID for holder
- Access to short history of finalised procedures with:
  - ✓ type of procedure (e.g. minor revision, notification, major revision, renewal, monograph revision)
  - ✓ end/finalisation date, outcome (i.e. CEP revised, CEP remains valid etc)
  - ✓ corresponding CEP number if any.

Full history information may not be available due to change of IT technology and tools



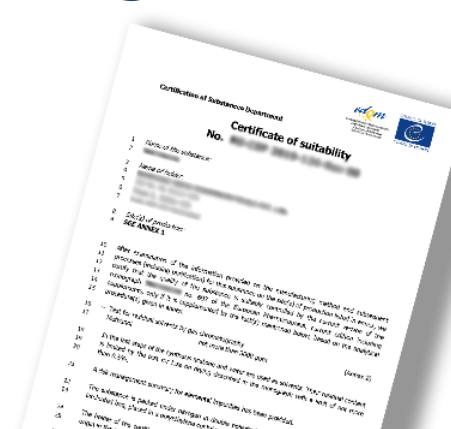
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# CEP information reported



# The CEP 2.0 – information reported

- CEP remains a « document », with a layout similar to the current one.
- Electronic document with a digital signature.
- Downloadable as a pdf-file or printed by CEP holders to share with their customers, for inclusion in Marketing Authorisation Application.
- No paper copy will be delivered by EDQM



# The CEP 2.0 – information reported

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Information which remains on the CEP 2.0 (unchanged):

- Subtitle
- List of class 3 solvents used in the last steps of the process and controlled by loss on drying
- Use of water in the last steps of the process → the quality of the water will be reported on the CEP
- Information on elemental impurities (Risk management summary (RMS) or statements on use/non-use)
- Container closure system and re-test period

# The CEP 2.0 – information reported

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Information which remains on the CEP 2.0 (unchanged):

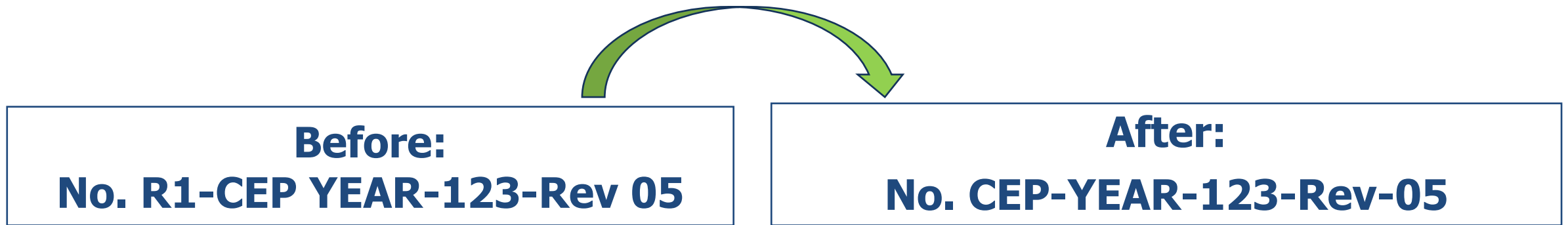
- Statement regarding production section of the monograph only when not assessed by EDQM (has to be addressed as part of the MAA)
- Statement on method of sterilisation when applicable
- For herbal CEPs, extraction solvents and excipients.

# The CEP 2.0 – information reported

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What will change:

- numbering system: the increment due to renewal is no longer part of the number



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# CEP 2.0 Implementation



# The CEP 2.0 – implementation timeline

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Coexistence of “*old format*”, “*hybrid format*” and “*new format*” CEPs for certain period of time

Q3 2023:

- *New format* CEPs for any new CEP and at renewal
- *Hybrid format* after revision of existing dossiers when there is no impact on the specification reported on the CEP
- Valid *Old format* CEPs (= current layout) will remain
- Possibility for CEP holders to submit a special type of revision to move to *New format* CEP for existing ones – optional (at later stage).

- The *old format* corresponds to CEPs as granted till the implementation of CEP 2.0
- This means that no CEP will be granted with the *old format* after the implementation of the CEP 2.0
- CEPs granted before this date will still be valid until they get revised.



# Webinars for stakeholders

- Webinars were organised in May 2023 to present the CEP 2.0 and to share information on changes foreseen, one for Authorities (restricted access) and two for CEP holders and CEP users (no restriction, open to CEP holders, authorities, MAH etc).
- Recording of the webinar for CEP users is available on the EDQM website as a training material together with the slides used

<https://www.edqm.eu/en/-/title>





## Online training

### The CEP 2.0 – Webinar for CEP holders and CEP users

#### Target audience

This webinar is of interest to CEP applicants, holders and users, including manufacturers and competent authorities.

 [WATCH NOW](#) (Duration: 1 hours, 57 minutes)

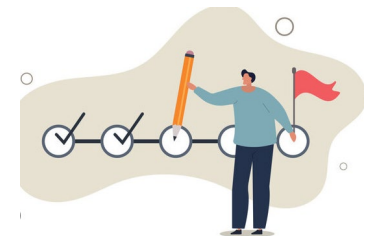
 [Download the presentations](#)

- > The CEP 2.0 Webinar for CEP holders and CEP users presented by the EDQM
- > Introduction to Organisation Management Service (OMS) presented by EMA

# Next steps

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- Q2-Q3 2023 work on various aspects on-going within DCEP for implementation :
  - Preparation of the update of databases: certification database and authorities database, digitally signed eCEP in the EDQM database, new numbering system for CEPs
  - Preparation of the changes in working methods/procedures, CEP templates, assessment.
- Communication and training campaign will continue, to explain and clarify the new expectations regarding CEP dossiers and also the changes to the CEP document.



# Next steps

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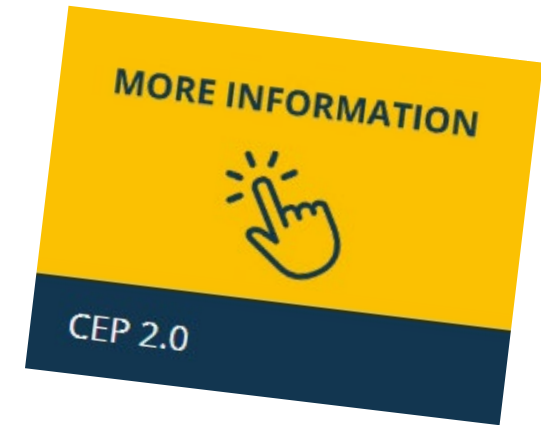
- Mass mailing to all CEP holders and applicants to inform about the CEP 2.0 and the new requirements.
- FAQs will be prepared based on the questions received.
- Publication on the EDQM website of the list of competent authorities and organisations with a MoU or confidentiality agreement for sharing assessment reports.
- Updates and revised documents will be published regularly in a dedicated webpage on the EDQM website [here](#).
- Follow-up webinar will be organised to gather feedback after implementation.



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# Any question, need of clarification or suggestions?

- Consult the EDQM website for supportive guidance documents
- The Certification Department provides support through the EDQM helpdesk.



# Acknowledgments

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- Nataliia MOSTRIANSKA (EDQM)
- Andrea MELLONI (EDQM)
- Nimet Filiz (EDQM)

# Thank you for your attention



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