CEP 2.0: CEP Holder’s perspective

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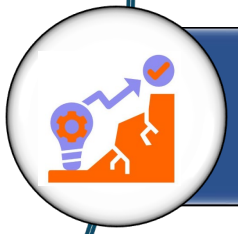
AGENDA

Overview on CEP 2.0 implementation

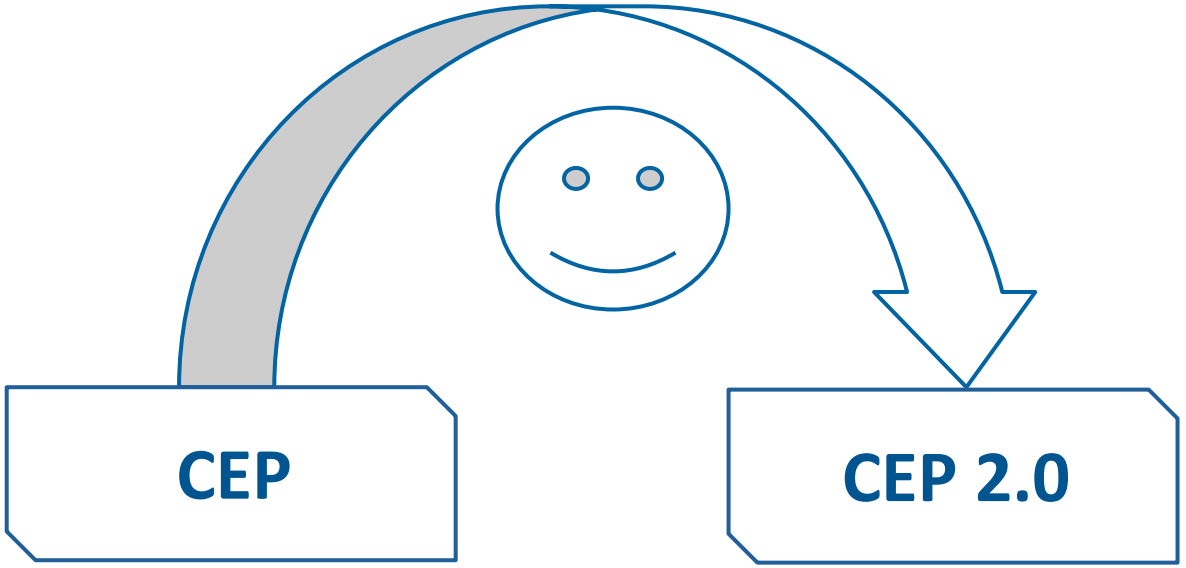
Benefits of CEP 2.0



Impact of Changes (MAH & CEP Holder’s Perspective)

Recommendations & way forward

Overview on CEP 2.0 implementation: Why the change?



- To meet the emerging needs of stakeholders
- To ease the registration activities linked with CEPs with increased transparency
- To increase the acceptance of CEP with Global Regulatory authorities

Overview on CEP 2.0 implementation: What is changed ?

- Similar Layout but with digitally signed Electronic format (pdf) and use of online share point portal for CEP issuance
- Numbering of the CEP changed from 3 block to 2 block code

2-block code
CEP 20XX-XXX-Rev 00

- Declaration Access Box replaced with Letter of Access

XXXX, as holder of the certificate of suitability
RX-CEP XXXX-XXX .. Rev XX for XXXX

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(sl if known)*

The holder also certifies that no significant changes to the operations as described in the ~EP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holde!):*

(< FROM CEP HOLDER ON HEADED PAPER>)

LETTER OF ACCESS TEMPLATE

[Date]

CEP number (including revision number):

Name of the substance:
Subtitle (if applicable):
CEP holder: [name and address]

The CEP holder hereby authorises the marketing authorisation holder/applicant to refer to the abovementioned CEP in support of the following marketing authorisation application(s) or marketing authorisation variation(s):

[Name of product (if known)]

[Name of applicant or marketing authorisation holder]

The CEP holder commits to batch-to-batch consistency, to share information in order to enable the abovementioned marketing authorisation holder/applicant to take full responsibility for an evaluation of the suitability of this substance for its intended use, and to inform them of any relevant changes to the CEP dossier.

Signature of the CEP holder

[Name and function]

[Signature]

Overview on CEP 2.0 implementation: What is changed ?

- Mandatory inclusion of EMA SPOR OMS Org ID and Loc ID in the application form for all sites.

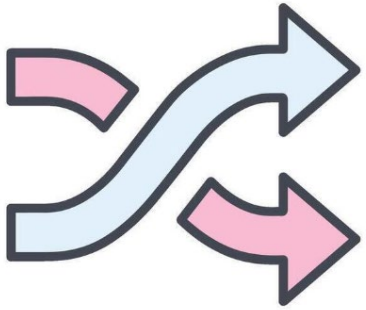
Organisation ID	Organisation Name ▲	Country	Location ID	City	Address	Postcode	Location status
ORG-100013412	European Medicines Agency	Netherlands	LOC-100020264	Amsterdam	Domenico Scarlattilaan 6	1083 HS	ACTIVE
ORG-100013412	European Medicines Agency	Netherlands	LOC-100020260	Amsterdam	P.O. Box 71010	1008 BA	ACTIVE
ORG-100013412	European Medicines Agency	Netherlands	LOC-100018793	Amsterdam	Orlyplein 24	1043 DP	INACTIVE
ORG-100006175	European Medicines Agency	United Kingdom	LOC-100010800	London	30 Churchill Place	E14 5EU	INACTIVE

- **Certain Policy changes:**
  - ✓ No more systematic revision of CEPs in case of major changes (unless there is change in information annexed to CEP).
  - ✓ No more expiry date to CEP (although the renewal process remains mandatory).

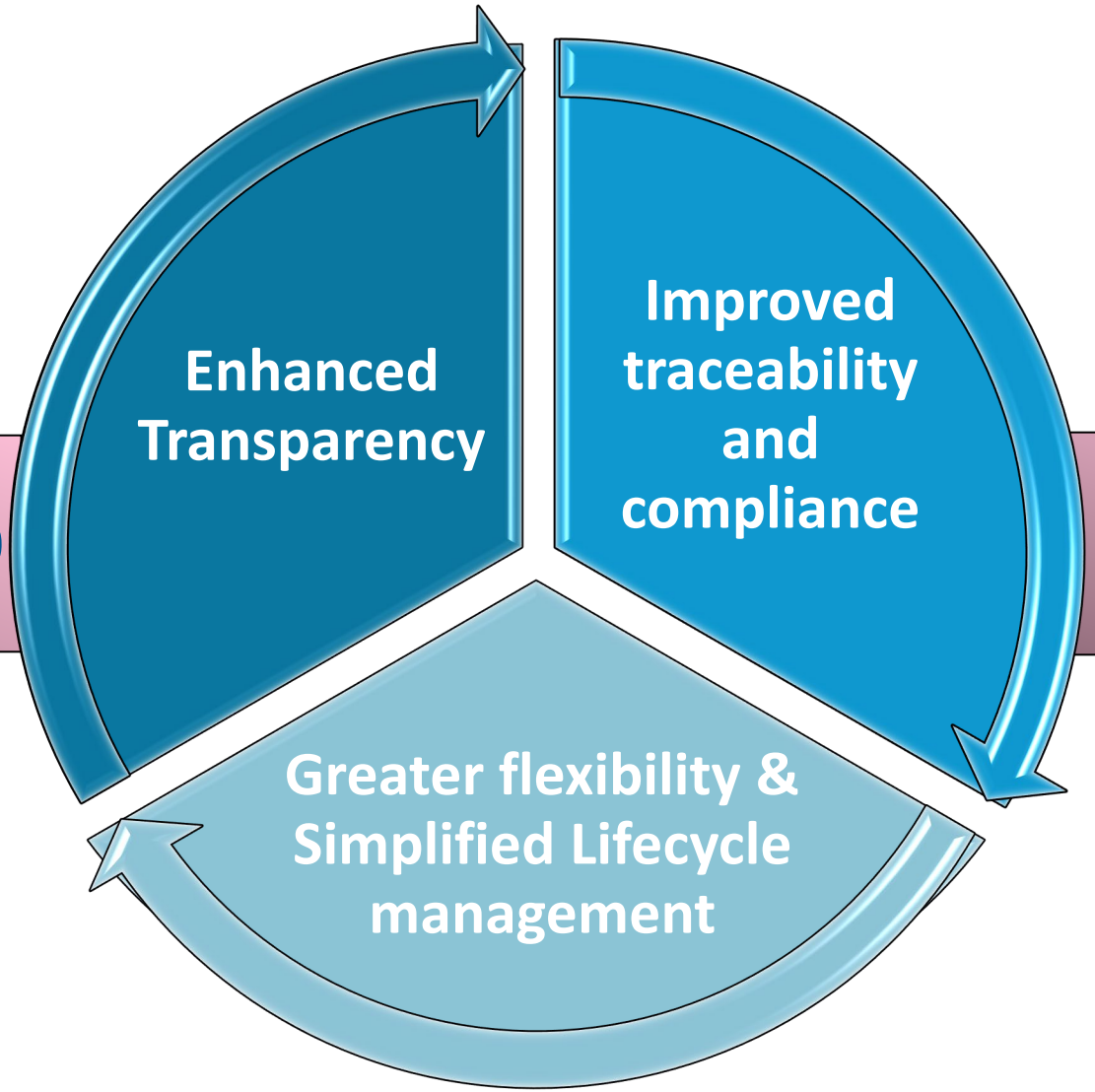
Overview on CEP 2.0 implementation: What is changed ?

- Enhanced responsibility for the information-sharing between CEP holders & MAH - A specific sentence on this obligation of CEP holder on CEP/ LOA/ Application form.
- Technical information appended to the CEP: Specification, additional methods etc.
- Updated expectations w.r.t. the content of certain CTD sections.

Benefits of CEP 2.0



Transition to CEP 2.0



Better Global Regulatory alignment

Benefits of CEP 2.0 : : Enhanced Transparency

Technical information appended to the CEP

- Specification (3.2.S.4.1) applied by CEP applicant/ Holder and approved by EDQM in tabulated format with clarity on acceptance criteria (Ph. Eur./ Inhouse/ Region specific)
- Use of an unambiguous chemical name of in-house impurities, ICH Q3D, Nitrosamine impurities.
- Additional methods (as per section3.2.S.4.2) needed to control the quality of the substance.

Benefits of CEP 2.0 : : Enhanced Transparency

Improved content of CTD sections

- Inclusion of Maximum Daily Dose (MDD), route of administration and treatment duration considered for the control strategy development **(EPAR/SmPCs/ Martindale**) and release specification (3.2.S.1.3)
- Process water quality compliance as per EMA "Guideline on the quality of water for pharmaceutical use (EMA/CHMP/ CVMP/ QWP/ 496873/ 2018)" and Ph. Eur. (3.2.S.2.3)
- Inclusion of grade specific process & quality parameters like polymorphic forms/ Particle size / Sterility test etc. (3.2.S.4.1)
- Grade specific / climatic zone specific / container closure specific stability data inclusion (where applicable) (3.2.S.7)

Benefits of CEP 2.0 : : Improved traceability and compliance

Use of the EMA SPOR/OMS database

Manufacturing site details reflected on CEP, listed with the Organization (**Org**) ID & Location (**Loc**) ID, issued basis Authentic and validated information from officially issued documents by local Govt.

Revision in manufacturing site information first updated and approved in EMA SPOR/ OMS database.

Benefits of CEP 2.0 : : Improved traceability and compliance

CEP Holder's / Applicant's obligation

Reinforcement of CEP holder's responsibility on information-sharing with MAH – Inclusion of commitment in application form, LOA & a specific sentence on CEP.

Compliance of information-sharing obligation will be checked during EDQM GMP inspections.

Benefits of CEP 2.0 : : Improved traceability and compliance

Improved look of public certification database & Authorities database

- Publication of history of procedures in the public Certification database, for user awareness on changes.
- Resource optimization: Grant of restricted access of Authority database to Eu Regulatory authorities.
- Extension of Authority database access to Regulatory authorities beyond EU Regions under confidentiality agreements/ MoU.

Benefits of CEP 2.0 : Greater flexibility & Simplified Lifecycle management

More flexibility - storage conditions/ temperature

- 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.
- Restrictive storage conditions with respect to temperature may be accepted and reflected on the CEP together with the re-test period, when supportive stability data is available.
- Different re-test periods and storage conditions can be proposed within the same CEP application (e.g., different re-test period depending on the container closure system or climatic zone).

Benefits of CEP 2.0 : Greater flexibility & Simplified Lifecycle management

Reduction in CEP revisions/ MA variations

- No more systematic revision of CEPs in case of major revisions.
- No more expiry date to CEP (however the renewal process remains mandatory).
- Reduced burden of MA variations on MAH and Regulatory authorities.

Impact of changes: MAH perspective

Enhanced acceptance by MAH due to greater transparency in the information annexed to CEP

Provision of issuance of Letter of Access (LOA) similar to the ASMF procedure is welcomed

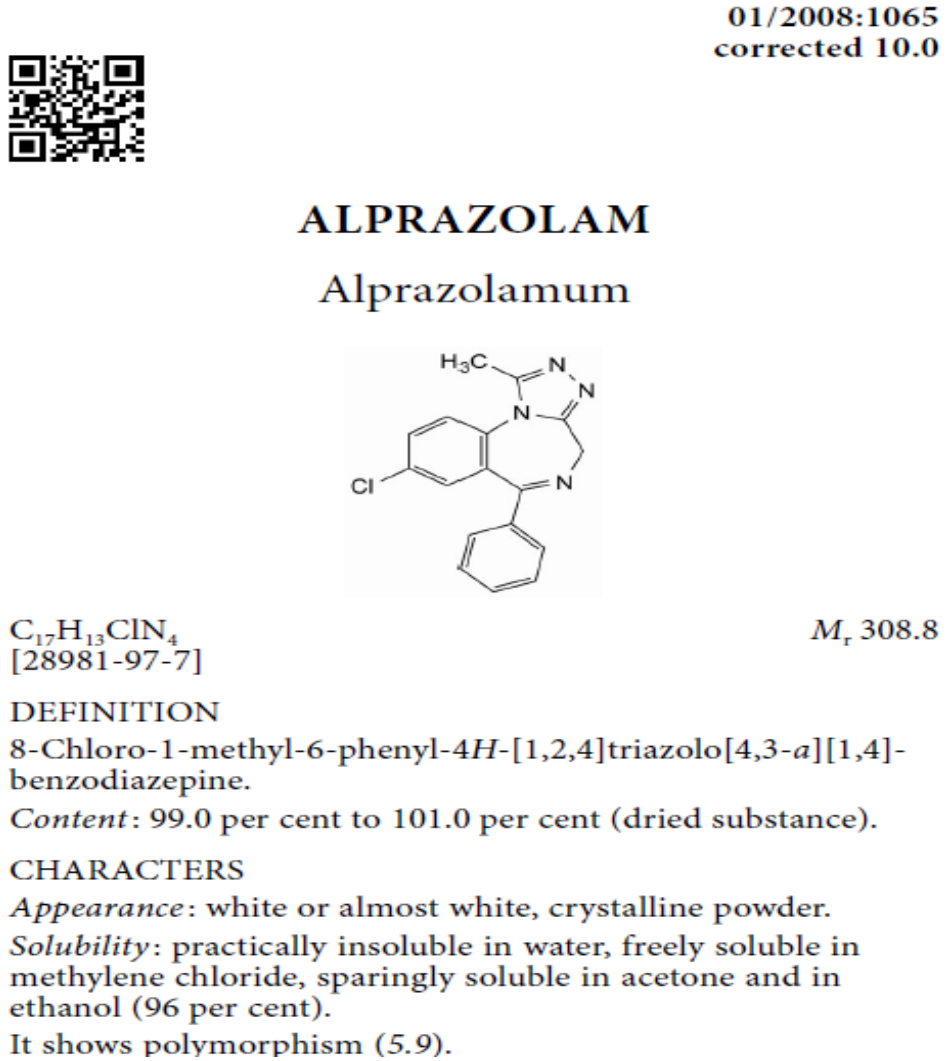
Inclusion of CEP Holders obligation on CEP & LOA gives greater assurance on authenticity of data

Reduction in MA variations & resource saving due to reduction in CEP version changes, related to drug substance life cycle

Impact of changes: Implementation Challenges (CEP Holder's Perspective)

Management of specification changes as per CEP 2.0 incase of existing approved CEPs; e.g., test for counter Ion content, Polymorphism etc.

Option to retain polymorphic identity test with specifying form and corresponding 2Θ values or to delete the polymorphic identity test.
Retention of test for counter ion content not recommended unless specified in Monograph.



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ALPRAZOLAM

Alprazolamum

$C_{17}H_{13}ClN_4$ [28981-97-7] M_r 308.8

DEFINITION

8-Chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]-benzodiazepine.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (*5.9*).

Impact of changes: Implementation Challenges (CEP Holder's Perspective)

API development for Global Regulatory markets: Difference in MDD based on the type of formulation / different region specific PIL

EDQM can evaluate the possibility to provide option to consider the most stringent MDD for determination of control strategy for global acceptance

Impact of changes: Implementation Challenges (CEP Holder's Perspective)

Topiramate

Brazil Package Insert of Reference drug- Topamax:

- **Tratamento adjuvante em epilepsia**

Adultos

A dose mínima eficaz é 200 mg ao dia. Em geral, a dose total diária varia de 200 mg a 400 mg, dividida em duas tomadas. Alguns pacientes eventualmente poderão necessitar de doses de até 1600 mg por dia, que é a dose máxima. Recomenda-se que o tratamento seja iniciado com uma dose baixa, seguida por uma titulação da dose até que se chegue à dose adequada.

O tratamento deve ser iniciado com 25 a 50 mg, administrados à noite, durante uma semana. Posteriormente, a intervalos de 1 ou 2 semanas, a dose deverá ser aumentada de 25 a 50 mg/dia e dividida em duas tomadas. A titulação

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Martindale monograph:

used for the prophylaxis of migraine (see Headache, p. 560.1) and, as a modified-release combination preparation with phentermine hydrochloride, in the management of obesity (p. 560.2; see under Phentermine, p. 2366.2, for details of doses).

For both adjunctive and monotherapy of **epilepsy**, the initial oral dose of topiramate is 25 to 50 mg at night for 1 week increased thereafter by increments of 25 or 50 mg at intervals of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for *adjunctive therapy* is 200 to 400 mg. When used as *monotherapy*, usual doses range from 100 mg daily to a maximum of 500 mg daily.

USFDA Label:

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

NDA 020505-S-050 Topamax (topiramate) oral tablets (25mg, 50mg, 100mg and 200mg)
NDA 020844-S-041 Topamax (topiramate) sprinkle capsules (15mg, and 25mg)
FDA Approved Labeling Text dated September 2012
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Table 2: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 Years

Weight (kg)	Total Daily Dose (mg/day)* Minimum Maintenance Dose	Total Daily Dose (mg/day)* Maximum Maintenance Dose
Up to 11	150	250
12 - 22	200	300
23 - 31	200	350
32 - 38	250	350
Greater than 38	250	400

EPAR- Qsiva:

About the product

This application for Qsiva was submitted initially under the name Qnexa. The product had also the investigational name "VI-0521" and is authorised in the US under the name of Qsymia. It contains phentermine/topiramate which is frequently abbreviated throughout this report as PHEN/TPM.

Qsiva is a combination of phentermine and topiramate that contains lower doses of these components than are currently marketed world-wide as monotherapies for weight loss (phentermine) or other indications. The recommended dose of phentermine/topiramate contains phentermine 7.5 mg and topiramate 46 mg, which is approximately one-fourth the maximum approved daily dose of phentermine (37.5 mg; 30 mg free base) in the United States and one-tenth the maximum approved daily dose of topiramate (400 mg) in the United States and European Union. Full-dose

Impact of changes: Implementation Challenges (CEP Holder's Perspective)

EU /Other CEP referencing regions:

For existing CEPs, expectations from MAH to maintain additional tests under separate customer specific specification to avoid any change variation / major impact on MA

Impact of changes: Implementation Challenges (CEP Holder's Perspective)

Lack of sufficient awareness related to EMA SPOR/ OMS database with Intermediate manufacturers.

Results in resource involvement from API manufacturers to create awareness and over all delay in CEP application submission by API manufacturers.

Recommendations & way forward

- **Possibility of Retention of certain non pharmacopeial tests on the CEP;** e.g. Salt specific/ counter ion related tests, as these factors are considered as part of formulation development and MDD calculations where applicable, can be allowed to retain in the specifications under *'additional tests not required to be appended to CEP',* as it is intrinsic part of drug substance structure and control of the same will be beneficial for better control on the quality.

- **More trainings to the industry , handholding with Non Eu regulatory authorities,** to accept the EDQM review and approved CEP as it is without any additional region specific requirements , over & above CEP 2.0 scope.

- **EDQM to evaluate possibility of single CEP application for the APIs meant for sterile as well as non sterile use**. (e.g. Dexamethasone, Morphine)

- **EDQM involvement with Regulators for setting up similar review process for non pharmacopeial APIs/ ASMF procedures** for independent review and approval.

To Summarize…

- CEP >>>>> CEP 2.0 much needed transition
- Aligns with current expectations from MAH and Regulators
- Once transitioned, will ease Regulatory life cycle management
- Will Reduce the Regulatory burden on the Industry & will improve resource optimization
- Will ensure consistent quality standards & Patient safety
- Need of the hour: Periodic trainings for the Industry
- Continuous process: Handling of multiple CEP revisions & discussing the challenges with EDQM for appropriate solutions
- Close collaboration between Industry & Regulators will help achieving EDQM goal of increased global acceptance.


Thank You
For Your
Attention