

## Certification of Substances Department

July 2020

### IMPLEMENTATION OF THE EUROPEAN PHARMACOPOEIA SUPPLEMENT 10.3

The table at the end of this announcement provides a list of substances covered by a CEP and for which a revised monograph will be implemented on **1<sup>st</sup> January 2021** in Supplement **10.3** of the European Pharmacopoeia.

According to EU Directives 2001/83/EC and 2001/82/EC as amended, it is the responsibility of the manufacturer to comply with the current version of a Ph. Eur. monograph, and therefore to update the specification when a revised monograph is issued. In addition, the EDQM ensures that CEPs refer to the most recent version of a Ph. Eur. monograph at any time.

The need to submit information to EDQM following a revised monograph depends on the changes made to the monograph. Updates to the monographs are classified by EDQM into "**Case A**" and "**Case B**" and this influences the information required. In the list of revised monographs below, it is **indicated which classification ("Case A" or "Case B") is applicable**. In addition to this web announcement, EDQM, as a courtesy, will contact holders of CEPs with details of how to proceed for the dossiers impacted by the revised monograph(s). However it **remains the responsibility of the CEP holder to comply with the requirements of the monograph** and if necessary to update their respective applications at the latest for the implementation date of the revised monograph, regardless if they have been contacted by EDQM.

#### • **Case A:**

The specification of the substance should be updated according to the revised monograph. Unless the CEP holder has made reference to the "current version of the monograph" (without providing details on the Ph. Eur. tests and methods in the CEP application), the updated specification should be included in the next request for revision that is submitted to EDQM (minor, major or renewal of the certificate) and identified as such at that time (such an update will be free of charge). Where the CEP holder has made reference to the "current version of the monograph", the revised monograph should be implemented without the need to update the specification of the substance at the next request for revision.

#### • **Case B:**

This case concerns amendments to the monograph which require the submission of data to EDQM. An updated dossier demonstrating that the substance complies with the requirements of the revised monograph should be provided within three months of EDQM contacting the CEP holder. The company is asked to provide a Module 1 discussing shortly the changes made to the application. This module should also include a clarification whether all related substances are controlled using only the method described in the revised monograph and whether the substance contains any impurities which are not described in the revised monograph (and which are found above the reporting threshold of the Ph. Eur. General Monograph 2034).

Module 3 should be updated to include, as necessary,

- A comparison of the impurity profile of the substance with the updated transparency list of the monograph (**3.2.S.3.2 "Impurities", 3.2.S.4.5 "Justification of Specifications"**)
- A discussion on the suitability of the revised monograph to control any impurities which are not described in it
- An updated substance specification/test methods description (**3.2.S.4.1 "Specifications", 3.2.S.4.2 "Analytical Procedures"**)
- Certificates of analysis of 2 batches with reference to the revised monograph (**3.2.S.4.4 "Batch Analysis"**)
- Validation and cross-validation data when an in-house method is used as an alternative to a new test method in the monograph (**3.2.S.4.3 "Validation of Analytical Procedures"**).

In Case B scenario, the CEP applications require an update and therefore any holder of a CEP for a substance of the "**Case B**" list below is expected to provide the requested information to EDQM, even if no specific request for information was received (this may happen namely when information regarding a change of contact person has not been submitted to EDQM in a timely manner).

If the requested information has already been presented in the approved dossier, a simple letter stating this is deemed sufficient.

Failure to update the CEP application and to provide data to EDQM may challenge the validity of the concerned granted CEP, or delay the on-going evaluation process of the concerned application.

Upon receipt, the data will be reviewed within 3 months and the CEP holder will be informed of the outcome of the evaluation. The assessment may also result in a **revised CEP** being granted.

This procedure is free of charge, unless the holder submits, at the same time, a request for other changes.

Name of the substance (monograph number)	Classification	
	CASE A	CASE B
Acamprosate calcium (1585)		X
Acetylcysteine (0967)		X
Adrenaline (2303)	X	
Betamethasone (0312)	X	
Betamethasone dipropionate (0809)	X	
Bleomycin sulfate (0976)	X	
Borax (0013)	X	
Calcium carbonate (0014)	X	
Calcium chloride dihydrate (0015)	X	
Celiprolol hydrochloride (1632)		X
Codeine monohydrate (0076)	X	
Codeine phosphate hemihydrate (0074)	X	
Cyanocobalamin (0547)		X
Dexamethasone (0388)	X	
Dexamethasone acetate (0548)	X	
Dipotassium phosphate (1003)	X	
Disodium phosphate dodecahydrate (0118)	X	
Epinastine hydrochloride (2411)		X
Epirubicin hydrochloride (1590)	X	
Ergotamine tartrate (0224)	X	
Fluoxetine hydrochloride (1104)		X
Hawthorn leaf and flower dry extract (1865)		X
Indapamide (1108)	X	
Isoconazole (1018)		X
Isoconazole nitrate (1017)		X
Ketoconazole (0921)		X
Labetalol hydrochloride (0923)	X	
Letrozole (2334)		X
Magnesium chloride hexahydrate (0402)	X	
Magnesium hydroxide (0039)	X	
Magnesium oxide, heavy (0041)	X	
Magnesium sulfate heptahydrate (0044)	X	
Mexiletine hydrochloride (1029)		X
Minocycline hydrochloride dihydrate (1030)	X	
Moxifloxacin hydrochloride (2254)	X	
Mupirocin (1450)	X	
Mupirocin calcium (1451)	X	
Mycophenolate sodium (2813)		X
Ofloxacin (1455)		X
Omega-3-acid triglycerides (1352)		X
Passionflower herb dry extract (1882)		X
Pentobarbital sodium (0419)		X

Potassium chloride (0185)	X	
Potassium clavulanate (1140)	X	
Potassium clavulanate, diluted (1653)	X	
Prednisolone acetate (0734)	X	
Prednisone (0354)	X	
Primidone (0584)		X
Sodium acetate trihydrate (0411)	X	
Sodium carbonate (0773)	X	
Sodium dihydrogen phosphate dihydrate (0194)	X	
Sodium hydrogen carbonate (0195)	X	
Sotalol hydrochloride (2004)	X	
Streptomycin sulfate (0053)		X
Tramadol hydrochloride (1681)	X	
Tramazoline hydrochloride monohydrate (1597)		X