How are Pharmacopoeial monographs written, interpreted and changed?

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Tasmanian Alkaloids

Overview

- How to read and interpret monographs
  - The format and style of monographs
  - How to interpret
    - When you have a different impurity profiles
    - Or want to use an alternative methods
- Updating monographs

Example Monographs

- Use Codeine Phosphate Active Pharmaceutical Ingredient (Drug Substance) as example
  - EP/BP “Codeine Phosphate Hemihydrate”
  - USP “Codeine Phosphate”
  - *Same drug substance, different names*

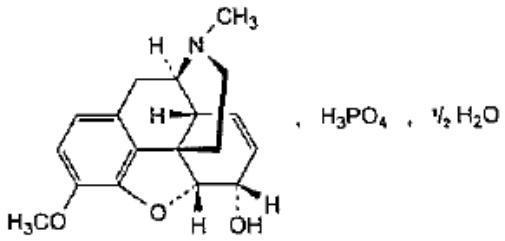
Use EP (Ph. Eur.) monograph as the example on following slides

Monograph Scope

01/2011:0074

CODEINE PHOSPHATE HEMIHYDRATE

Codeini phosphas hemihydricus



$C_{18}H_{24}NO_7P,½H_2O$ M_r 406.4
[41444-62-6]

DEFINITION

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate hemihydrate.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or small, colourless crystals.

Solubility: freely soluble in water, slightly soluble or very slightly soluble in ethanol (96 per cent).

Edition: Monograph Number

Structure, Molecular Formula, Molecular weight, CAS Number

Assay Specification is listed here (not at the assay test instructions)

"Characters" are not tested parameters, (but appearance is normally tested)

Identification Tests

IDENTIFICATION

First identification: *B, E, F.*

Second identification: *A, C, D, E, F, G.*

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution. Dilute 1.0 mL of solution S (see Tests) to 100.0 mL with *water R*. To 25.0 mL of this solution add 25 mL of *water R* then 10 mL of *1 M sodium hydroxide* and dilute to 100.0 mL with *water R*.

Spectral range: 250-350 nm.

Absorption maximum: at 284 nm.

Specific absorbance at the absorption maximum: about 38 (dried substance).

Two sets of Identity tests to chose from

Follow the general EP method detailed at this chapter reference

Reagents are described in chapter 4

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dissolve 0.20 g in 4 mL of *water R*. Add 1 mL of a mixture of equal volumes of *strong sodium hydroxide solution R* and *water R* and initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod and cooling in iced water. Wash the precipitate with *water R* and dry at 100-105 °C. Examine the dried precipitate prepared as discs using *potassium bromide R*.

Comparison: *Ph. Eur. reference spectrum of codeine.*

C. Dissolve 0.20 g in 4 mL of *water R*. Add 1 mL of a mixture of equal volumes of *strong sodium hydroxide solution R* and *water R* and initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod and cooling in iced water. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at 155 °C to 159 °C.

D. To about 10 mg add 1 mL of *sulfuric acid R* and 0.05 mL of *ferric chloride solution R2* and heat on a water-bath. A blue colour develops. Add 0.05 mL of *nitric acid R*. The colour changes to red.

E. Loss on drying (see Tests).

F. Solution S gives reaction (a) of phosphates (*2.3.1*).

G. It gives the reaction of alkaloids (*2.3.1*).

Tests for Quality

TESTS

Solution S. Dissolve 1.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 25.0 mL with the same solvent.

pH (*2.2.3*): 4.0 to 5.0 for solution S.

Specific optical rotation (*2.2.7*): – 98 to – 102 (dried substance).

Dilute 5.0 mL of solution S to 10.0 mL with *water R*.

Specification and test method reference combined

"dried substance" means correct for loss on drying in the result calculation

Sulfates (*2.4.13*): maximum 0.1 per cent.

Dilute 5 mL of solution S to 20 mL with *distilled water R*.

Loss on drying (*2.2.32*): 1.5 per cent to 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.350 g in a mixture of 10 mL of *anhydrous acetic acid R* and 20 mL of *dioxan R*. Titrate with *0.1 M perchloric acid* using 0.05 mL of *crystal violet solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 39.74 mg of $C_{18}H_{24}NO_7P$.

STORAGE

Protected from light.

No reference to a general chapter.
No calculation given.
Your analytical knowledge is required to interpret the test

Special storage restrictions provided, e.g. light & temperature

Impurity Test

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined and 0.100 g of *sodium octanesulfonate R* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *codeine impurity A CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (d). To 0.25 mL of the test solution add 2.5 mL of reference solution (a).

Column:

- *size:* l = 0.25 m, Ø = 4.6 mm;
- *stationary phase: end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 1.08 g of *sodium octanesulfonate R* in a mixture of 20 mL of *glacial acetic acid R* and 250 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 2 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 10 µL.

Run time: 10 times the retention time of codeine.

Relative retention with reference to codeine (retention time = about 6 min): impurities B and E = about 0.7; impurity A = about 2.0; impurity C = about 2.3; impurity D = about 3.6.

System suitability: reference solution (d):

- *resolution:* minimum 3 between the peaks due to codeine and impurity A.

Chromatography general chapter (2.2.29)

- System suitability (SS) requirements
- Calculation of SS parameters
- Allowable adjustments to methods

Reference standard “CRS” needed – may be purchased from EDQM or use your own secondary standard

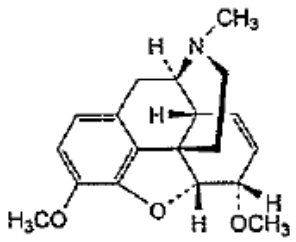
Example column provided in the EDQM Knowledge Database (on line)

Impurity Limits

- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);
- *sum of impurities B and E*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.4 per cent);
- *impurities C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
- *sum of impurities other than A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Impurity codes used, with structure listed below

Do not consider peaks below 0.05%



A. 7,8-didehydro-4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (methylcodeine),

USP Monograph

Codeine Phosphate

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot {}^1/_2H_2O$ 406.37
Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-, phosphate (1:1) (salt), hemihydrate.
7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate [41444-62-6].
Anhydrous 397.37 [52-28-8].

» Codeine Phosphate contains not less than 99.0 percent and not more than 101.5 percent of $C_{18}H_{21}NO_3 \cdot H_3PO_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store up to 40° as permitted by the manufacturer.

USP Reference standards ⟨11⟩—
USP Codeine Phosphate RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Neutralize a solution (1 in 50) with 6 N ammonium hydroxide, and add silver nitrate TS: a yellow precipitate of silver phosphate is formed, and it is soluble in 2 N nitric acid and in 6 N ammonium hydroxide.

Acidity—Dissolve 100 mg in 20 mL of water, and titrate with 0.010 N sodium hydroxide to a pH of 5.4, using a pH meter: not more than 1.0 mL of 0.010 N sodium hydroxide is required.

Water, *Method I* ⟨921⟩: not more than 3.0%.

Chloride—To 10 mL of a solution (1 in 100), acidified with nitric acid, add a few drops of silver nitrate TS: no opalescence is produced immediately.

Sulfate—To 10 mL of a solution (1 in 100) add a few drops of barium chloride TS: no turbidity is produced immediately.

Limit of morphine—Dissolve about 50 mg of potassium ferricyanide in 10 mL of water, and add 1 drop of ferric chloride TS and 1 mL of a solution of Codeine Phosphate (1 in 100): no blue color is produced immediately.

Chromatographic purity—Using Codeine Phosphate, proceed as directed in the test for *Chromatographic purity* under *Codeine*, except to use a mixture of 0.01 N hydrochloric acid and dehydrated alcohol (4:1), instead of dehydrated alcohol, to prepare *Solution A*, *Solution B*, and *Solution C*.

Assay—Dissolve about 1 g of Codeine Phosphate, accurately weighed, in 50 mL of glacial acetic acid, warming slightly if necessary to effect solution, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 39.74 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4$.

- USP is similar, but not the same:
- TLC method for Impurities
- Water content, not Loss on Drying
- No Specific Optical Rotation

USP Chapter numbers in <xx> brackets

What is Not in the Monograph

- Specifications which are related to the route of manufacture and thus are not generic, e.g.:
  - Control of Residual Solvents
    - EP 5.10 and USP <467> specifically describe limits for solvent residues and example test methods
    - You apply limits for the solvents used in your manufacturing process
- Customer specific tests, e.g. particle size

Other Pharmacopoeias

- All Pharmacopoeia are different!
  - Check the fine print – e.g. the method chapters
- Indian Pharmacopoeia: closely aligned with BP
  - HPLC system suitability requirements are different
- Japanese Pharmacopoeia: tests are similar to a mix of EP & USP, with different method details and limits
- Example, pH of a codeine phosphate in solution:
  - EP: 4.0 – 50, IP: 4.2 – 5.0, JP: 3.0 – 5.0

Summary

- Monographs are historical documents
  - Based on the impurity profile and methods used by the sponsor of the monograph
- The impurities list may not cover those generated by a new synthetic process
- The methods may not be not be current best practice

Different Impurity Profiles

- Drug substances may be made by different synthetic routes
- Each route could have different related substance impurities
- Some monographs will only address one (the first) synthetic route
- Some monographs will have required and optional impurity limits
- Some monographs could have different methods and limits to chose from

Optional Related Substances

EP Codeine Phosphate Hemihydrate monograph

IMPURITIES

Specified impurities: *A*, *B*, *C*, *D*, *E*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *F*, *G*.

Note the two types of Impurities: “Specified” and the optional “Other Detectable Impurities”

If you have other impurities, limits are established in the general monograph 2034, (which is similar to ICH Q3A)

Use of Alternative Methods

- Alternative methods are preferred in some situations, e.g.
  - Monograph has a TLC test, you have a “better” HPLC test for impurities
  - HPLC method may not detect all impurities in your drug substance
  - Method uses hazardous reagents, e.g. chloroform

Use of Alternative Methods - USP

- USP General Notices
  - Allow the use of an equivalent or superior method

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* ⟨1225⟩ and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

Alternative procedures should be submitted to USP for evaluation as a potential replacement or addition to the standard (see section 4.10, *Monographs*).

Use of Alternative Methods - EP

- EP do not have the same general statement as USP, so:
- Alternative methods may be used, but there may be regulatory filing updates required
- You must assure yourselves and Customers that the alternative method produces results which are equivalent to the EP method
  - If your Customer tests by the EP method, your product must meet specification

UPDATING A MONOGRAPH

Updating Monographs Overview

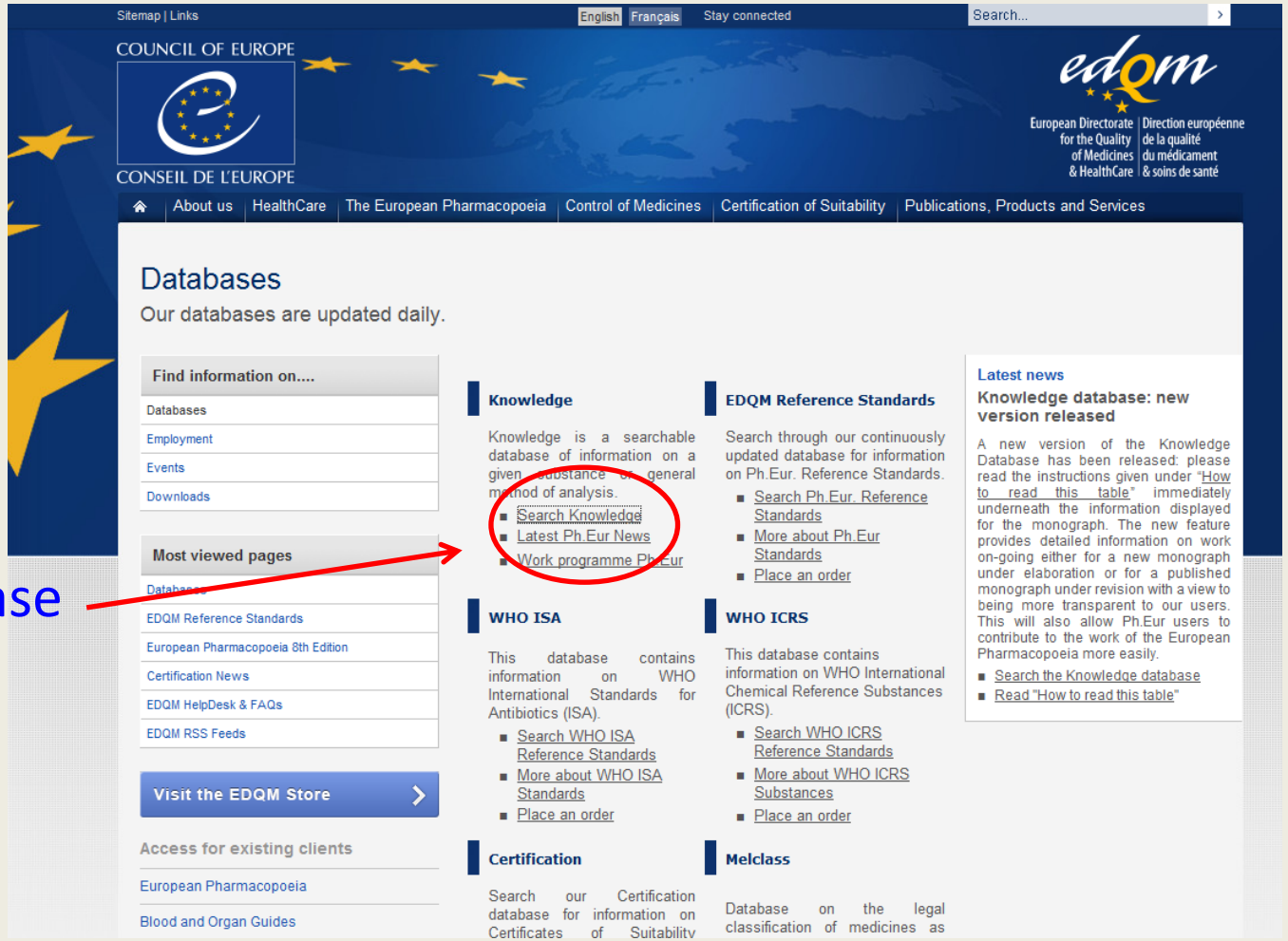
- Monographs can be updated, but it will take a considerable period of time
- EP & USP use Technical Teams from Industry to review and advise on proposed updates
- Update proposals are published for public comment before implementation
  - EP: Pharmeuropa: http://pharmeuropa.edqm.eu/home/
  - USP: USP-PF: http://www.usppf.com/pf/login

EDQM Knowledge Database

To check if an EP monograph is already in revision, check the Monograph Database: http://www.edqm.eu/site/edqm-databases-10.html

Knowledge Database

Search for the monograph



EP Monograph Status

If a revision is underway – the blue section is visible

Reference Standards available

HPLC Column that is recommended for the method

Detailed view of Codeini phosphas hemihydricus.

Status	In use
Monograph Number	00074
English Name	Codeine phosphate hemihydrate
French Name	Codéine (phosphate de) hémihydraté
Latin Name	Codeini phosphas hemihydricus
Pinyin Name	
Chinese Name	
Pharmeuropa	
Published in English Supplement	7.0
Published in French Supplement	7.0
On-going	Revision
State of work	0
Pharmeuropa	
Description	Related substances test.
Chromatogram	Not available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
International Harmonisation chapter 5.8	NO

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price
	C2500000	Codeine - reference spectrum	1	n/a	79 EUR
	Y0000334	Codeine impurity A	4	15 mg	79 EUR

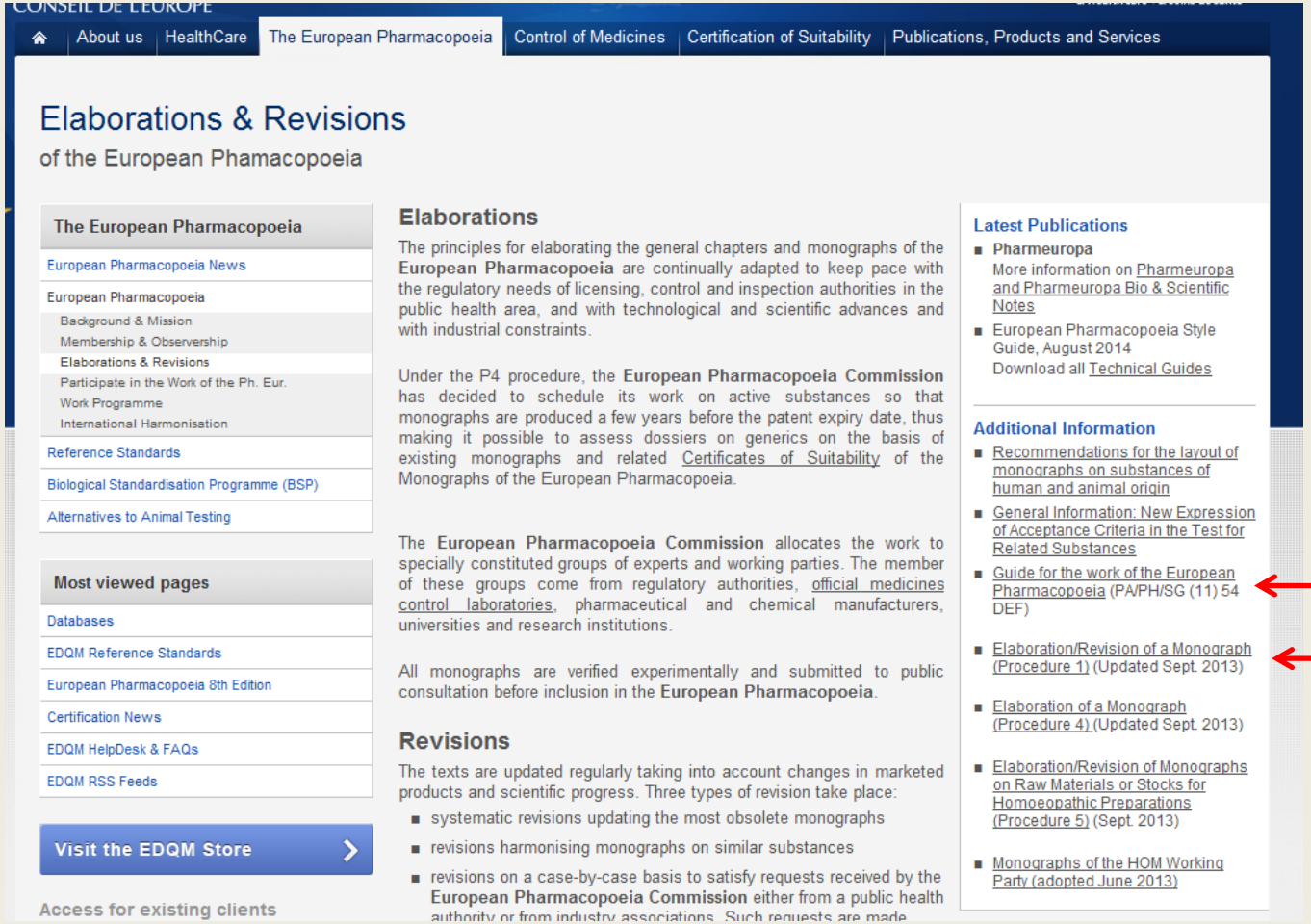
Trade Names

To be used in test(s)	Brand Name
Related substances	Column : l = 0.25 m, diam. = 4.6 mm, 5 µm, Spherisorb C 8

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
74	Codeine phosphate hemihydrate	ALKALOIDA CHEMICAL COMPANY ZRT. HU 4440 Tiszavasvari	R1-CEP 2006-199-Rev 00	30/01/2013	VALID		Chemistry

EP Updates Process

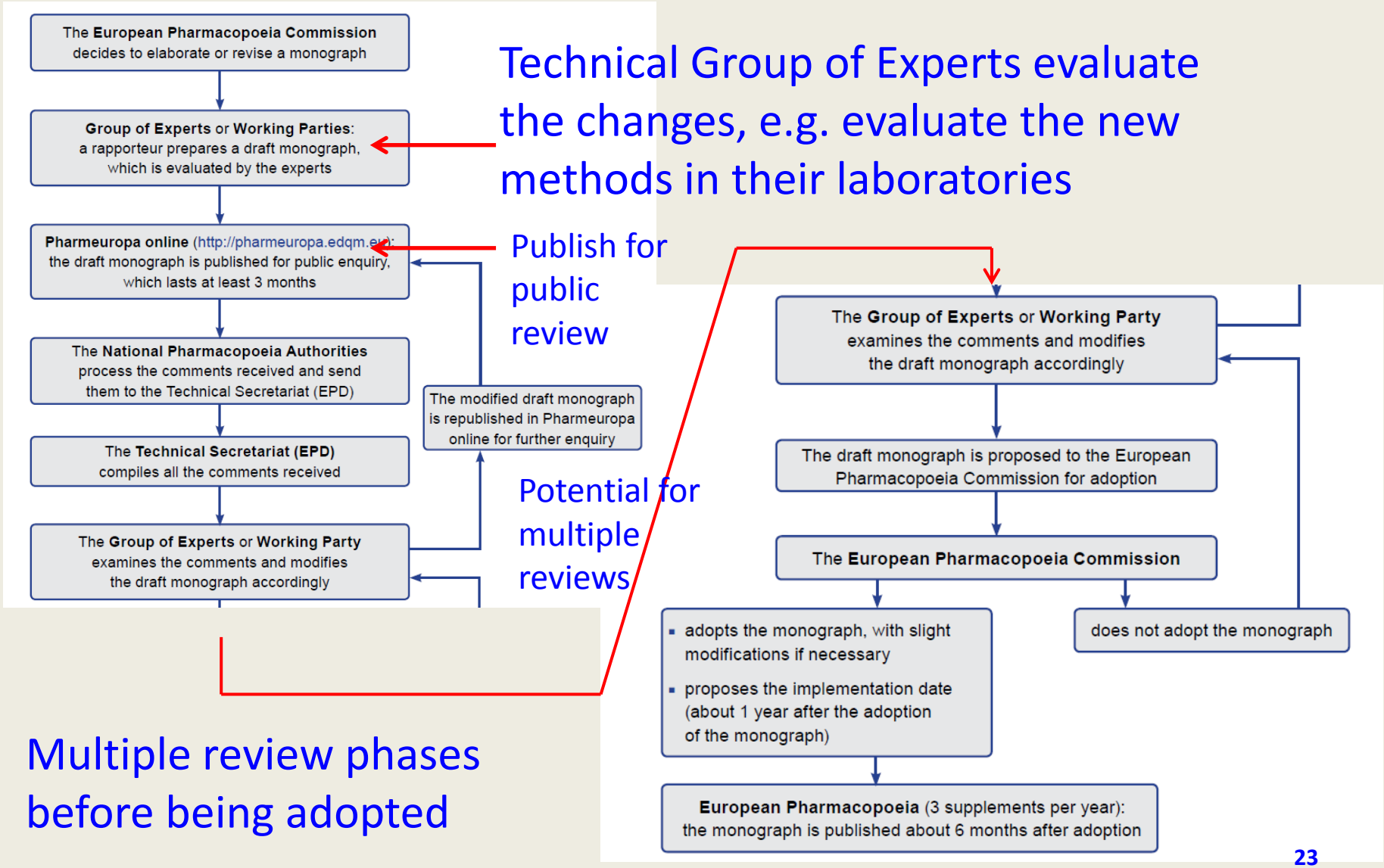
http://www.edqm.eu/site/european-pharmacopoeia-elaboration-revisions-606.html



Guide to the process

Revision Flowchart

EP Update Steps

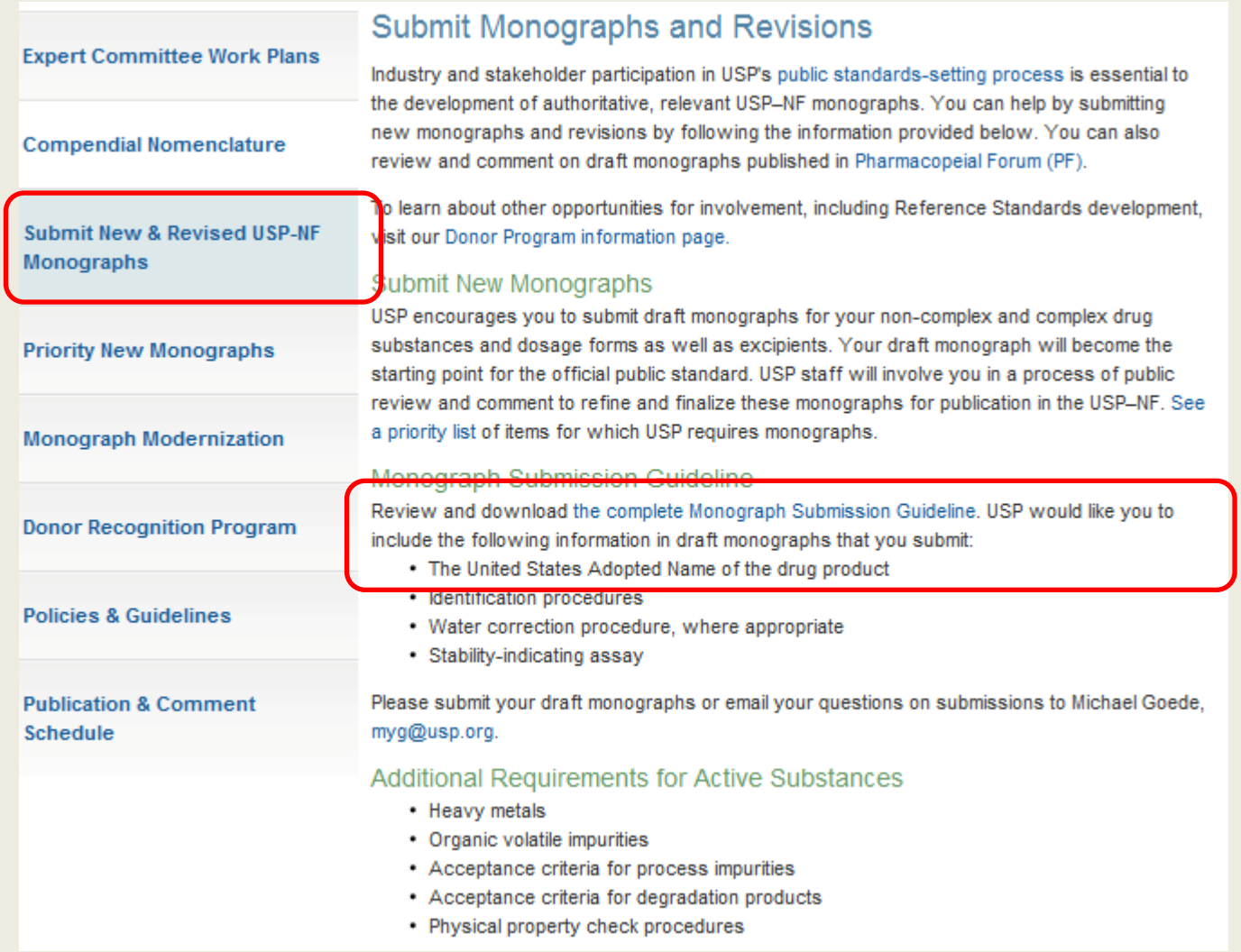


EP Internal Update Process

- The EDQM manages both the EP and the EU drug substances regulatory filings
  - Certificates of Suitability to the EP or “CEP”
- The CEP application process requires an evaluation of the suitability of the monograph method to your drug substance
- If the EP method is not suitable, and you use a different method, the EDQM internally will initiate a review of the monograph

USP Monograph Updates

USP Monograph Update



USP Modernization

- Expert Committee Work Plans
- Compendial Nomenclature
- Submit New & Revised USP-NF Monographs
- Priority New Monographs
- Monograph Modernization
- Donor Recognition Program
- Policies & Guidelines
- Publication & Comment Schedule

USP Seeks Submission of Proposals for Monograph Modernization

To continue to provide high-quality public standards, USP is modernizing many existing monographs across our compendia. We seek industry collaborators to assist in this effort.

USP intends to modernize these monographs as soon as possible via traditional submission (e.g. manufacturer of article) or USP's internal laboratory efforts.

USP would like to receive submissions for monographs denoted as "High Priority" within 90 days of the high priority designation. "High Priority" monographs for which USP does not receive submissions may be directed to our laboratory for development.

Ways in which you may help include:

- Submitting your current analytical procedure and supporting validation data
- Providing the names of impurities and FDA-approved acceptance criteria to be incorporated into the modernization revision developed by USP's internal labs
- Providing sample amounts of the article for USP's internal lab development.

For more information, visit our Key Issue: Monograph Modernization page.

Select the below link to view chemical medicines and excipients monographs requiring modernization:

VIEW LIST

For more information or to inform us of your participation, please contact the Standards Acquisition Manager, Michael Goede at myg@usp.org.

Useful Links

- EDQM Databases: http://www.edqm.eu/site/edqm-databases-10.html
- USP Development
- http://www.usp.org/usp-nf/development-process?destination=node%2F1091
- USP Modernisation
- http://www.usp.org/usp-nf/development-process/monograph-modernization?destination=node%2F1088

Thank You