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

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What GMP inspectors expect on Reference Standards

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Regulatory background for APIs: EU GMP Part II, Chapter 11

- 11.17:
  - Primary reference standards should be obtained as appropriate for the manufacture of APIs.
  - The source of each primary reference standard should be documented.
  - Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations.
  - Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Regulatory background for APIs: EU GMP Part II, Chapter 11

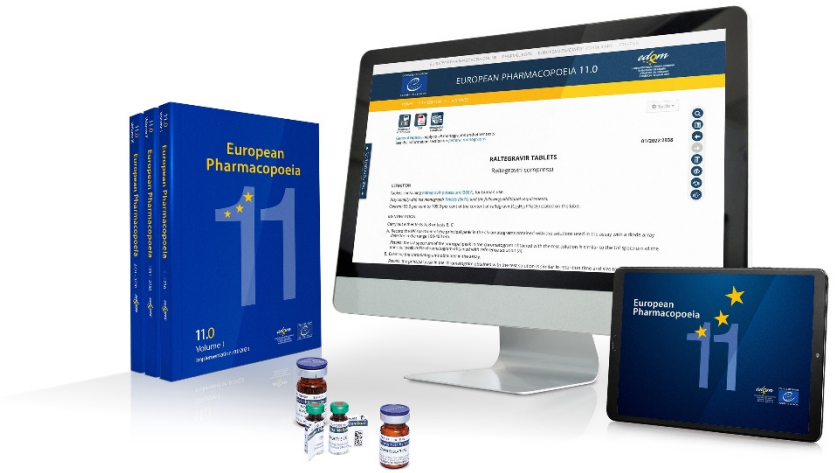
- 11.18:
  - Where a primary reference standard is not available from an officially recognized source, an “in-house primary standard” should be established.
  - Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard.
  - Appropriate documentation of this testing should be maintained.
- 11.19:
  - Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored.
  - The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard.
  - Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

Regulatory background: Ph. Eur

- General notice 1.6: Reference Standards
  - Certain monographs require the use of reference standards, which can be chemical reference substances (CRSs), herbal reference standards (HRSs), biological reference preparations (BRPs) or reference spectra
  - See also general chapter 5.12*. Reference standards*
  - Unless otherwise stated, the reference standards referred to in texts are alone authoritative in case of arbitration

What the inspector check (amongst other thing...)

- Availability of current Ph. Eur. RS(s)
- Availability of secondary reference standards (working standard, WS - if primary not routinely used)
- Evidence of appropriate qualification of WS against RS
- “Shelf life”/re-qualification of WS
- Appropriate storage conditions & labelling
- ...



Deficiencies on reference standards in EDQM inspections

- Review of 148 EDQM inspection reports (2011-2022):
  - ➢ 41 deficiencies concerning Reference Standards identified, of which 4 classified as “major”, 37 as “other”
    - Ratio decreasing (in ~44% of inspections in 2011-2015, but in ~14% in 2016-2022)
    - Less or no deficiencies observed during re-inspections – companies adopting requirements

Types of deficiencies: Ph. Eur. Reference Standards

- Ph. Eur. reference standard for the active substances/impurities, as required by the specific monograph, were not available

- Reconstituted or diluted solutions of primary reference standard were stored for further use, but suitability of this approach was not demonstrated by the user

Types of deficiencies: secondary reference standards

- Only internally manufactured secondary reference standards (working standards) were used however they were not qualified against Ph. Eur. reference standards

- The suitability of working standards was not adequately determined by comparison against CRS. Only an identification test by IR was performed

- The in-house working standard XXX was qualified against the Ph. Eur. CRS as per the specifications of Ph. Eur. 7.0. The same standard was used for the validation of the new HPLC methods of the XXX monograph as updated in Ph. Eur. 8.2 without having been tested against the new specifications

Types of deficiencies: secondary reference standards

- There was no evidence that the secondary reference standard was appropriately re-qualified

- Lack of traceability in relation to qualification of the working standards: the certificate of analysis of the working standard did not include reference to the batch number of the official Ph. Eur. CRS against which the WS had been qualified

Types of deficiencies: in-house primary reference standards

- The reference standards manufactured by the company were subject to characterisation studies and used as primary reference standards, but no qualification against the official reference standard or equivalency studies were conducted.

- Appropriate testing was not performed to establish fully the identity and purity of the primary reference standards in the absence of an officially recognized source.

- Only the first batch of internally manufactured reference standard was established as an “in-house primary reference standard” with a full physicochemical characterization, and used to qualify a batch of working standard. After that, the suitability of the subsequent batches of working standards was only verified against the previous working standard batch and not established against a fully characterised primary reference standard

Types of deficiencies: storage of reference standards

- Inappropriate storage conditions:
  - improper temperature
  - no alarm or alert
  - stored with inappropriate labelling

- The Eur. Ph. XYZ reference standard was stored at room temperature while the recommended storage temperature was +5°C
- There was no monitoring or recording of max/min refrigerator temperatures where the Eur. Ph. standard of impurity A was stored (recommended storage temperature: +5°C)
- The fridge used to store the reference standards was not temperature monitored

Types of deficiencies: validity of CRS

- Batch Validity Statement for reference standards from EDQM was not periodically checked on the EDQM website

Catalogue Code	P0300000	
Name	Paracetamol CRS	Batches
Current batch number	4	batch 4 is valid at this date
Unit quantity per vial	50 mg	Print BVS
Number of vials per sales unit	1	RS webshop
Used in monograph(s)	0049	

BATCH VALIDITY STATEMENT
EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS (CRS) & (BRP)
This Batch Validity Statement has to be used in conjunction with Ph. Eur. general chapter 51200 Reference Standards.

Name	Paracetamol CRS
Catalogue code	P0300000
Batch number*	4
Assigned value	n/a
Validity	Batch 4 is valid at the printing date: 2021-6-7
Additional information	
Storage conditions	Recommended EDQM storage conditions for unopened containers : +5°C+/-3°C
Safety data	Safety Data Sheet is available from the detailed view or upon request.
Leaflet	Click on the hyperlink to download the leaflet containing the instructions for use, click to download the leaflet
Origin	Click on the hyperlink to download the origin to check if import permit is required in your country, click to download Origin Of Goods.pdf

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- Sotirios Paraschos, Inspector, EDQM

Thank you for your attention

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