European Pharmacopoeia Reference Standards
Handling, dispatch, where to find useful information and other practicalities

2019 Training Session
“The European Pharmacopoeia”
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Before ordering

Ordering

Labelling

What is expected from users

Proving validity

Monitoring & Stability programmes

Shipping & Storing

Safety

Other source of information & FAQ
BEFORE ORDERING

Consult the online catalogue.

⚠️ Specific catalogue for Ph. Eur. / ISA and ICRS (WHO)

BEFORE ORDERING

Available online.

Updated daily. English only.

• For searching database: https://crs.edqm.eu
BEFORE ORDERING

Several possibilities to search for a RS:

- CAS are provided for information only and are not independently verified.
- Possibility to print the entire catalogue (interface with IT system in xml)
- See next slide

Terms and conditions of supply


List of new batches and new items

http://crs.edqm.eu/db/4DCGI/web_catalog_news

RS withdrawn from sale in the past 12 months

http://crs.edqm.eu/db/4DCGI/web_catalog_olds
BEFORE ORDERING

Prepare for customs and reception in your laboratory

New: composition to declare is now provided (!!! anticipate)

- SDS
- Origin of goods
- Proposed HS code
- EDQM Dispatch and storage conditions
- Availability

BEFORE ORDERING

Necessary documents in some cases:

- For **precursors**, **psychotropic** and **narcotic** substances: an original import permit to be sent to the EDQM

- For **biological material**: please check that you have the import permit (e.g. USDA permit)

- Some specific documents available from website:
  - Specific import form for Brazil
  - Letter replacing CoA
  - Legal Framework and Diplomatic Status of Reference Standards for Customs Purposes

- Pending issue: the country of origin!
Ordering

ORDERING

➢ Ph.Eur. RS can be ordered directly from EDQM:

➢ Care should be taken when ordering from other sources:
ORDERING

- EDQM does not have authorised distributors.

- EDQM is able to provide a list of organisations or companies known to re-sell EDQM products. This list is available through the website.

When an order is sent, you have 24 hours to correct or cancel the order.

Then, the order is blocked 24 hours for preparation (no possible change).

We privilege door-to-door shipment.
ORDERING

- Always have a close look to the AoR
- Shipping dates are known at the time of parcel preparation, not before
- Impossible to make door-to-door for some destinations because of shipping companies restrictions (even if requested at order stage!!)
- Ice: delivered at the closest “customs” airport!
- Chase your broker, if any (especially for ice / dry ice) & ANTICIPATE CUSTOMS ISSUES

Labelling
LABELLING

Includes:

- Primary label AND the pictogram;

- Secondary label (displaying the pictograms on the outer package);

- Leaflet
Safety information

Warning tag (if any)

Safety Information is also provided on the external secondary package: pictograms and warnings (in the language of the country).
Additional information is provided in the information leaflet:

* if used as an assay standard the following information is also given:
  - the assigned percentage content;
  - or, the content in mg or mL of the chemical entity in the container;
  - or, the assigned potency (for biological assays or microbiological assays) in units either per mg or per vial.

**This is not mentioned on the primary label anymore!**

* type-chromatograms, stoichiometric conversion factor, etc. are also available in the leaflet.
What is expected from the user

**WHAT IS EXPECTED FROM THE USER**

Immediately before using a Ph. Eur. Reference Standard, the following shall be checked:

- that the reference standard batch number be current at the time of use. Print the real-time batch validity statement (BVS) available online;
- that the container/closure system integrity be kept, i.e. absence of visible defects originating from shipping;
- that the reference standard after receipt has been stored at the conditions prescribed in the Ph. Eur. RS catalogue.
WHAT IS EXPECTED FROM THE USER

Moreover, allow the RS to equilibrate to lab temperature before opening. Use “as is” unless indicated in the leaflet.

Depending on the quantity in the vial, two main glass vials are used:

- for filling weights > 15 mg
  Brown glass vials (type 7 mL)

NB: also used for evaporation

- for filling weights > 15 mg
  V-vials facilitating the recovery of the powder

Proving validity
PROVING VALIDITY

No expiry date nor retest date is stated on the label

Use BVS

PROVING VALIDITY

Official Codeine imp. A CRS batch number = 5 => Check online BVS

Batch 5 is official at the time of printing

Also valid at the date of printing for sub-batches
PROVING VALIDITY

BUT: batch 4 is still valid until 10/31/2019 => Check online BVS
PROVING VALIDITY

At the time of analysis:
- Print out the BVS,
- Stick the peel-off label.

This ensure that you have used the official CRS at the time of use.

Monitoring & Stability programmes
**MONITORING & STABILITY PROGRAMMES**

**Why?**

  « A system is established and implemented to ensure the continued fitness-for-use of the European Pharmacopoeia reference standards. »

Once established, adopted and released for distribution, the Chemical Reference Substance (CRS) and Biological Reference Preparation (BRP) are checked regularly to demonstrate their suitability for the purposes for which they are intended (e.g. assay standard, external standard, identification, peak identification, system suitability...).

Designed to **detect** at an early stage any sign of degradation using appropriate analytical techniques.
**MONITORING & STABILITY PROGRAMMES**

✓ **When?**

The re-test programme is applied taking account of the known physico-chemical properties and stability data of the reference standards.

Reference standards are periodically tested for stability during storage.

The periodicity (from 12 to 60 months) and extent of re-testing depends on a number of factors including:
- intended use (qualitative / quantitative)
- physico-chemical properties & predicted stability information available
- mode of preparation (powder filling, lyophilisation, evaporation...)
- storage conditions

The re-test period may be prolonged or decreased with the support of sufficient data.

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**MONITORING & STABILITY PROGRAMMES**

✓ **How?**

The monitoring programme is designed to detect at an early stage any sign of decomposition using appropriate analytical techniques.

The focus is on the properties that may change during the life cycle of a CRS (*i.e.:* water content, purity by LC/GC/TLC, IR, UV).

The methods used are chosen from amongst those performed during establishment (so that baseline data are available) and chosen for their sensitivity & applicability to small quantities:
- micro-determination of water, gravimetric analysis (TGA)
- stability-indicating separation techniques (*LC*-UV/ELSD/CAD, TLC, GC)
- determination of molar purity (DSC)
- other specific tests for detecting impurities (NMR)
Criteria of acceptance/rejection:

Any significant differences observed compared to the establishment and to the previous examination(s) will lead to more extensive examination and if necessary to the re-establishment or to the establishment of a replacement batch. The maximum permitted variation is pre-defined depending on the use of the substance (e.g. identification by IR or TLC, SST, purity testing, assay...).

Example: CRS used for peak identification

All the impurities are still detected. The CRS is still suitable for its use but given the trend noted for impurities I and J, a quality replacement will be initiated.
MONITORING & STABILITY PROGRAMMES

Example: CRS used as external standard

Strong degradation for the filled and bulk substance.

The CRS was considered not suitable anymore for its intended purpose (i.e. impact on total amount of impurities and assigned value).
It was considered justified to suspend its distribution and to replace the batch.

Establishment Monitoring

Monitoring (filled)

Total impurities = 6.7%

Assigned content = 93.2%

Bulk

ISO 17034:2016
General requirements for the competence of reference material producers.
Chapt. 7.11. Assessment and monitoring of stability

ISO Guide 35:2017
Reference materials – Guidance for the characterization and the assessment of the homogeneity and stability of the material.
Chapt. 8. Assessment and monitoring of stability

✓ Why? New

ISO 17034:2016
General requirements for the competence of reference material producers.
Chapt. 7.11. Assessment and monitoring of stability

ISO Guide 35:2017
Reference materials – Guidance for the characterization and the assessment of the homogeneity and stability of the material.
Chapt. 8. Assessment and monitoring of stability

✓ Why?

"Concurrent approach" (real-time data) ➔ "Prospective approach" (predictive data)
MONITORING & STABILITY PROGRAMMES

✓ Why?

Multiple uses:
- to predict RS stability and to anticipate stability problems and therefore avoidance of RS recalls
- to help to identify/validate RS best storage / shipping conditions
- to better adjust the monitoring cycle
- to contribute to selection of the proper batch size

MONITORING & STABILITY PROGRAMMES

✓ What?

- Not applicable to all RS but to a selected number:
  - new RS/ existing RS
  - mixtures (SST, FPI)/ RS for quantitative use
  - LC/GC method available
  - RS adopted (homogeneity)
  - If sufficient batch size
How?

Types of stability studies:
- Not ICH stability
- Short-term & Long-term
- Different temperatures & different times

Design of stability studies: isochronous / continuous

Outcome

In case of issue affecting the proper use of the RS, a warning notice would be sent to those having ordered the RS with precise instruction.

Be careful if you use distributor.
Shipping and storing

**SHIPPING & STORING**

Packing materials (carton, boxes) are selected to minimise the risk of damage during transport and are compliant to the transport regulation prescription when applicable (IATA, ADR, IMDG).
Since Sept 2018, new packing materials have been introduced.

Specifications

+5°C => +1°C / +8°C
-20°C => -15°C / -25°C
Dry ice => -70°C / -50°C

For three days.

Dispatch at ambient temperature – short excursions from the long-term storage temperature during shipping are not considered to significantly affect the quality of the reference standard.

Dispatching conditions:
- Ambient temperature
- Under ice
- Under dry ice

Recommended storage conditions:
- +5°C or -20°C
- +5°C or -20°C
- -20°C or -80°C or Liq N₂
SHIPPING & STORING

EDQM storage conditions are established for **long-term** storage.

They are based on:

- Stability data,
- Data received from supplier of the bulk material,
- Monitoring,
- Literature,
- Ph. Eur. information.

User is free to adopt other storage conditions, under its own responsibility.

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SHIPPING & STORING

For optimal stability, storage temperature **one level below monograph prescription**.

- Room temperature -> +5°C
- +2 to 8°C -> -20°C (if possible, liquids...)
- Under -15°C -> -20°C
- -20°C -> -80°C (if possible)
- -50°C -> -80°C
- -80°C -> liquid nitrogen

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SAFETY

The external part of the vials containing Substances of Very High Concern is washed after manufacturing in order to protect staff using CRS.
SAFETY

Safety Data Sheet (chemicals) and Safety Data Statement (bio) are available from website.

You will also find a cumulative list of changes in the safety classification

NOTES:

• **Hazardous Chemicals**: the EDQM complies with UNECE globally harmonised system for classification and labelling of chemicals; as enacted in the EU.

SDSs are not provided for materials for which no hazard has been identified. In such cases, the hazard status of the material is available in the database and is also published on the shipping documents (with the text: "Hazard: none identified").

• **Biologicals**: Directive 2000/54/EC applies. EDQM issues Safety Data Statements if a hazard has been identified.

• Safety documentation is provided for occupational health only and is not part of quality standards.

Other sources of information & FAQ
OTHER SOURCE OF INFORMATION & FAQ

EDQM issues a monthly news & a monthly newsletter.

You can subscribe!

OTHER SOURCE OF INFORMATION & FAQ

It contains:

- **New** and **Replacement** batches
- **Removed** items

**NEW**: proposal under evaluation to keep it for additional 12 months in the catalogue for RA requirements in some countries

- **Change of sales unit**

- Information on changes of storage / shipping conditions

**NEW**: unless QA issue, changes are now announced in advance (change will occur on the 15th of the next month, if possible)

- Information on reference standards currently **out of stock**

**NEW**: when technical information is provided.
OTHER SOURCE OF INFORMATION & FAQ

FAQ
Directly available from the website.

TOP 10 Questions

• How can I obtain the CoA?

The EDQM does not provide certificate of analysis. Needed data are available in the information leaflet.

If you want to use the RS for another use, it is done under user’s responsibility.
OTHER SOURCE OF INFORMATION & FAQ

• I do not find the expiry date

No expiry date is provided. It is down to the user to demonstrate that the CRS/BRP used in an official Ph. Eur. test or assay was current at the time of use. The BVS is used for this purpose. In case of replacement batch, a validity is provided in the online catalogue. Therefore, it is recommended to purchase only a sufficient amount for analysis and to use the products as soon as possible. Once the container has been opened, weighing should be carried out immediately. Any further storage and re-use are not warranted.

OTHER SOURCE OF INFORMATION & FAQ

• I do not find the purity

RS are established for a precise intended use. In case the purity / assigned value / activity is not mentioned in the information leaflet, it means that this value is not needed to carry out the test/assay described in the related monograph(s) and therefore it is not provided.

!! it cannot be assumed to be 100%. The only exception is the purity of an impurity CRS, which can be estimated to be 100% for the tests of the monographs, if the EDQM has not stated the purity.
• There are two weights declared: on the label and on the leaflet, which one should I use?

In this case: freeze drying
qty = (API+excipients)

• I cannot recover the quantity from the vial

Each vial or ampoule is individually weighed during manufacturing and therefore contains a quantity sufficient for the prescribed use. Nevertheless, since there is usually a very low quantity, the product may be distributed between the inner surface and the rubber stopper. To avoid this problem and recover the full quantity, we usually recommend gently tapping the bottom of the vial several time in order to bring down the product. You can also use an anti-magnetic device to easily collect the powder. If the test / product allows, you can also work by differential weighing.
• The parcel arrived with cool packs thawed, is it suitable for use, may I obtain stability data?

Excursion outside recommended temperature usually does not jeopardise the quality of the RS.
In case of question, the EDQM will analyse the case with available data and will make a recommendation.
Stability data cannot be shared.

• Is there a QMS applied to RS? May I have a copy of the certificate?

The EDQM is ISO 9001 certified for the conduct of laboratory studies and RS production.

The EDQM laboratory is also ISO 17025 accredited for 20 analytical techniques used in the RS establishment.

Both certificates are available from the website.
• May I store the RS at different conditions than those stated in the catalogue?

The storage conditions mentioned in the catalogue are intended to preserve the integrity of the CRS during long-term storage. We base our conditions on supplier’s information, stability data (when available), monitoring data and bibliography. Our storage conditions are in most cases more stringent than those given in the monograph. Provided that you can demonstrate that the RS is fit for use at your chosen T°, nothing prevent you to do so.

• I want an old BVS / leaflet

For the leaflet, it can be provided on request.

For the BVS, it is not possible.
• I disagree with the CAS number provided in the catalogue

The CAS number provided are not independently verified by the EDQM. They are provided only to help the user and most of the time refer to the CAS number of the parent substance mentioned in the Pharmacopoeia, so it can differ.

• Other tips for the US
  - We do not provide packing list,
  - We provide proforma for customs clearance (invoice sent within 24 hours by mail),
  - FDA/TSCA Certification should be provided by the importer or an authorized agent of the importer (EDQM cannot provide it),
  - Gross weight is not mentioned on our invoices/proforma,
  - We cannot authenticate our document by a Chamber of Commerce,
  - We do not have a FDA registration N° - FDA product Id,
  - BE VERY PROACTIVE FOR BIOLOGICAL MATERIAL (e.g. insulin, lactose, etc.) – we cannot provide IND N°.
OTHER SOURCE OF INFORMATION & FAQ

Still a question?

Helpdesk
Directly available from the website with a direct link to FAQs

**NEW**: a completely new Helpdesk will be launched by the end of September.

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Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: [https://go.edqm.eu/Newsletter](https://go.edqm.eu/Newsletter)
LinkedIn: [https://www.linkedin.com/company/edqm/](https://www.linkedin.com/company/edqm/)
Twitter: @edqm_news
Facebook: @EDQM_CouncilofEurope