RADIOPHARMACY GMP
QC HPLC VALIDATION

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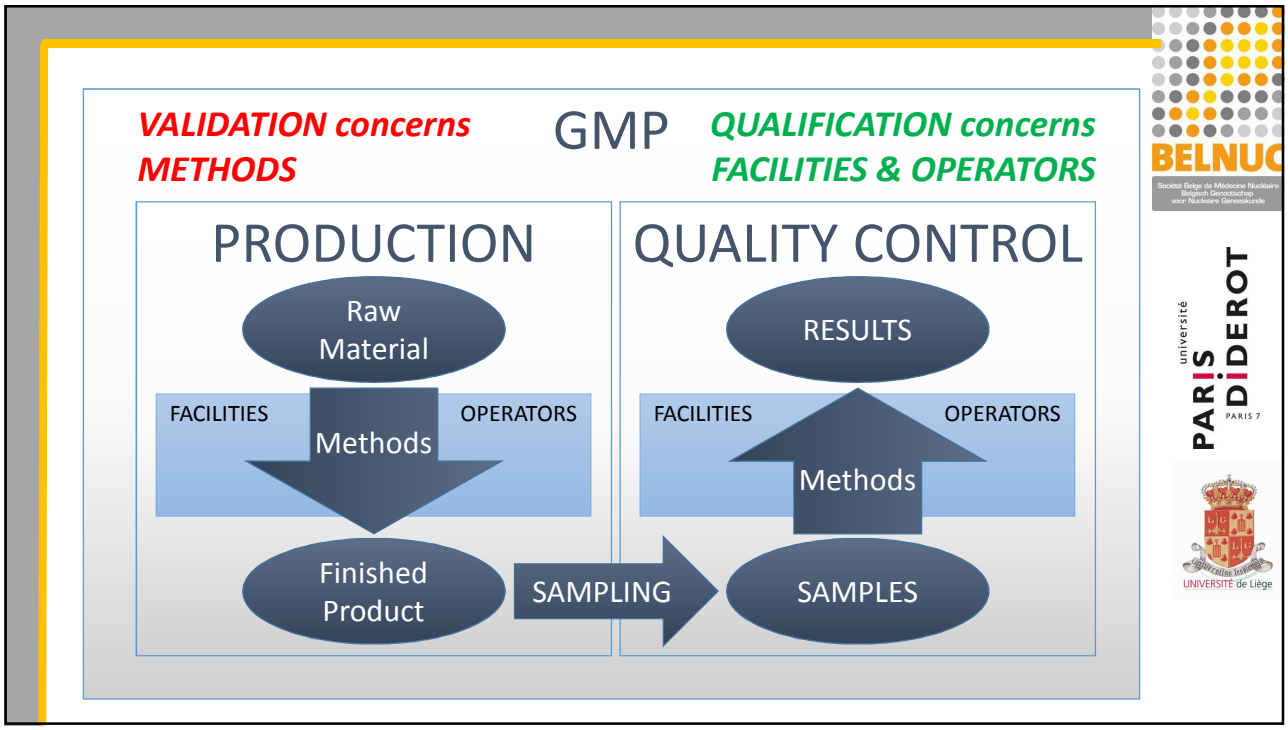
EudraLex - Volume 4 GMP Guidelines
Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification.
Good Manufacturing Practice is concerned with both production and quality control.

GMP

QC HPLC VALIDATION

EudraLex - Volume 4 GMP Guidelines
Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

ISO/IEC 17025:2005 5.4.5
Validation is the confirmation by examination and the provision of objective evidences that the particular requirements for a specific intended use are fulfilled.



Some references

- **ISO/IEC 17025** General requirements for the competence of testing and calibration laboratories
- **ISO 5725** Accuracy (trueness and precision) of measurement methods and results
- **ICH Q2** Validation of Analytical procedures

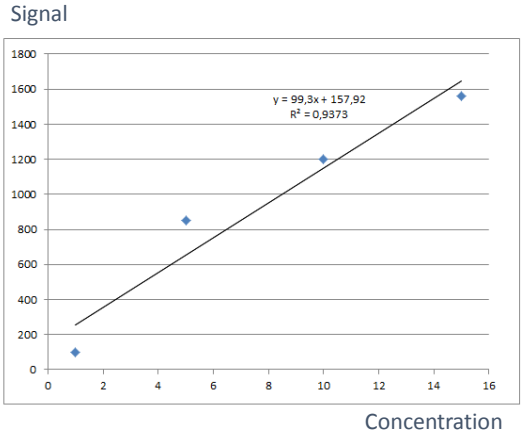
  Q2A: terminology ; Q2B: methodology
- Directive **96/23/CE** and decision **2002/657/CE**
- **EDQM** Technical Guide for the elaboration of monographs, 2011
- **STP PHARMA PRATIQUES, 13, 3, 2003** Validation of quantitative analytical procedure, Harmonization of approaches, Hubert P. et al.

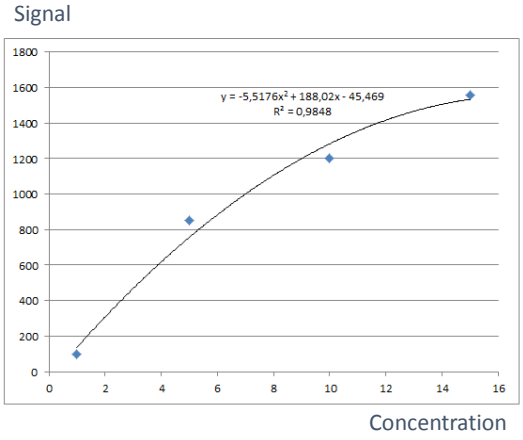
Criteria (ISO 17025)

- Specificity
- Accuracy = trueness + precision

  Total error = bias + variance
- Precision
  - Repeatability
  - Intermediate precision
- Limit of detection (LOD) and Limit of quantification (LOQ)
- Assay range
- Linearity (results vs conct.) <> response function (signal vs conct.)

Response function (calibration curve)





Criteria to be evaluated

Criteria \ Types of test	Identification	Assay	Impurity Limit Test	Impurity Quantitation
Specificity	YES	YES	YES	YES
Accuracy		YES		YES
Repeatability		YES		YES
Intermediate precision		YES		YES
Limit of Detection LOD			YES	YES
Limit of Quantification LOQ				YES
Linearity		YES		YES
Assay Range		YES		YES

3 important rules for the validation of analytical methods

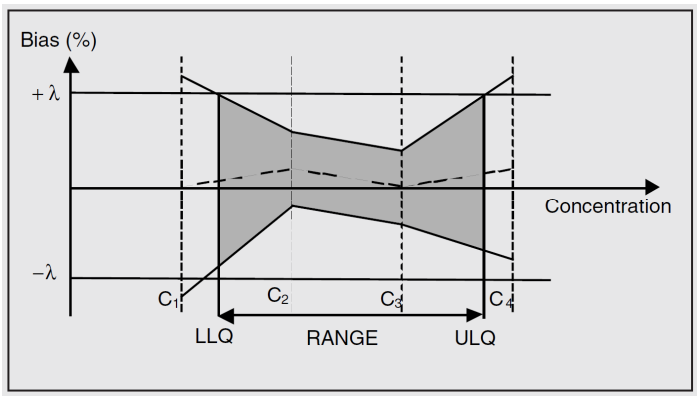
- Validation covers all operations of the methods from sampling (volume or weight) to generation of results (including mathematical transformations of data).
- Validation covers a finite range of concentration: extrapolation outside the range is not allowed.
- Validation is matrix specific. A new validation must be performed for each new matrix.

Validation of Eur. Pharm. methods ?

- The pharmacopoeial methods given in monographs and general chapters **have been validated** in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required.
- When implementing a pharmacopoeial method, the user must assess whether and to what extent **the suitability** of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

Accuracy profile as decision tool

λ = acceptance limit



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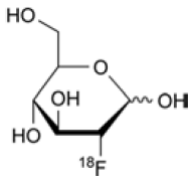
^{19}F-FDG limit test in ^{18}F-FDG

- *FLUDEOXYGLUCOSE (^{18}F) INJECTION*, European Pharmacopeia 8, 01/2014:1325: MAX: 0.5 mg/V V= maximum injected volume
- Liquid chromatography
  - Dionex ICS3000 with autosampler
  - Detection: amperometry (30°C)
  - Colonne Dionex Carbopac PA10 (25°C)
  - 1mL/min 100mM NaOH
  - Conditionnement: 1M NaOH every 3 injections



Criteria to be evaluated EP01/2014:1325

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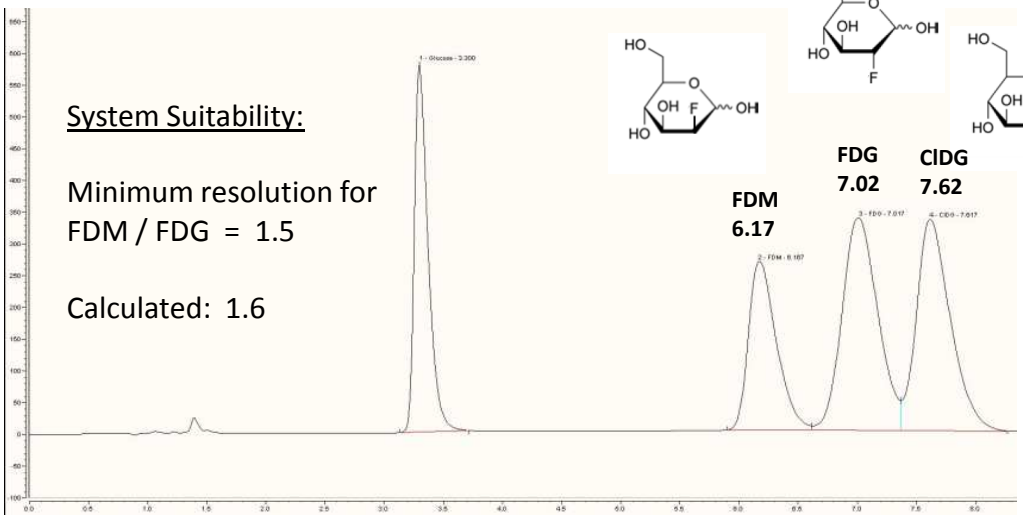
Assay Range		YES		YES

^{19}F-FDG limit test in ^{18}F-FDG



<u>System Suitability:</u>

Minimum resolution for FDM / FDG = 1.5

Calculated: 1.6

Quantitation at low concentration

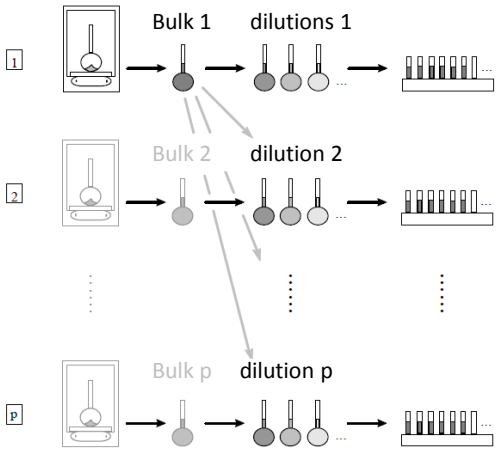
Types of test / Criteria	Identification	Assay	Impurity Limit Test	Impurity Quantitation
Specificity	YES	YES	YES	YES
Accuracy		YES		YES
Repeatability		YES		YES
Intermediate precision		YES		YES
Limit of Detection LOD			YES	YES
Limit of Quantification LOQ				YES
Linearity		YES		YES
Assay Range		YES		YES

PHASE 1 : organization

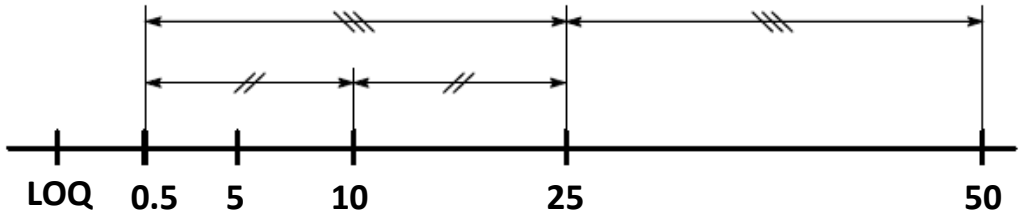
- Description of the analytical method
  - Information on product to assay and analytical system (HPLC, GC…)
  - Protocols for samples preparation
    - CS: calibration samples = solution of product in a suitable solvent
    - VS: validation samples = solution of product in the real matrix
- Concentration levels for CS et VS
- Validation plan. Ex. 3 days/1op or 2 days/2op
- Criteria to be evaluated

PHASE 2 : preparation of CS

SERIES (days)

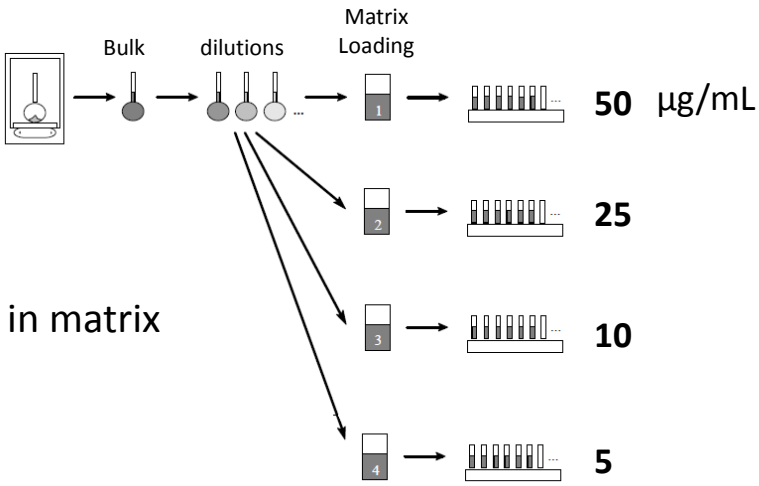


Example: preparation of CS for FDG



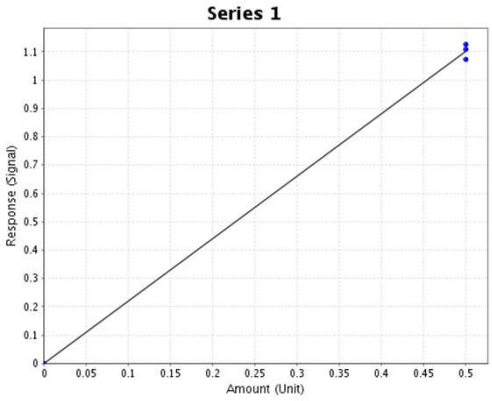
^{19}F-FDG in water µg/mL

PHASE 3 : preparation of VS

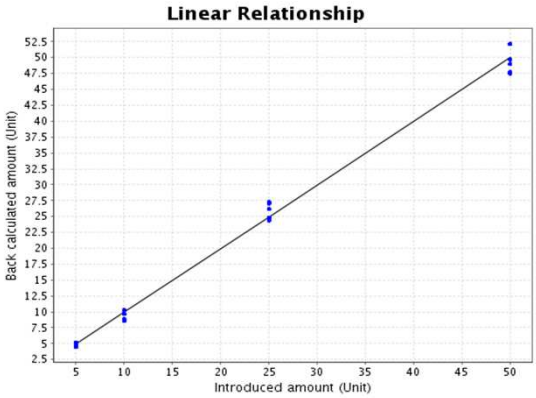


^{19}F-FDG in matrix

Results of injections of series

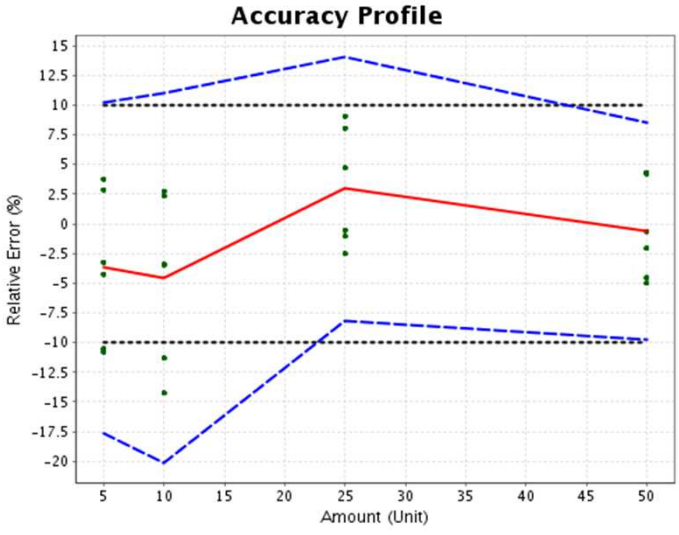


Linear Regression Through 0 fitted with the level 0.5 only ➔ calibration curve



Relationship between the introduced and the back-calculated amounts

Accuracy Profile



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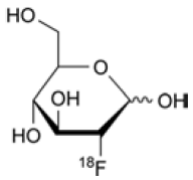
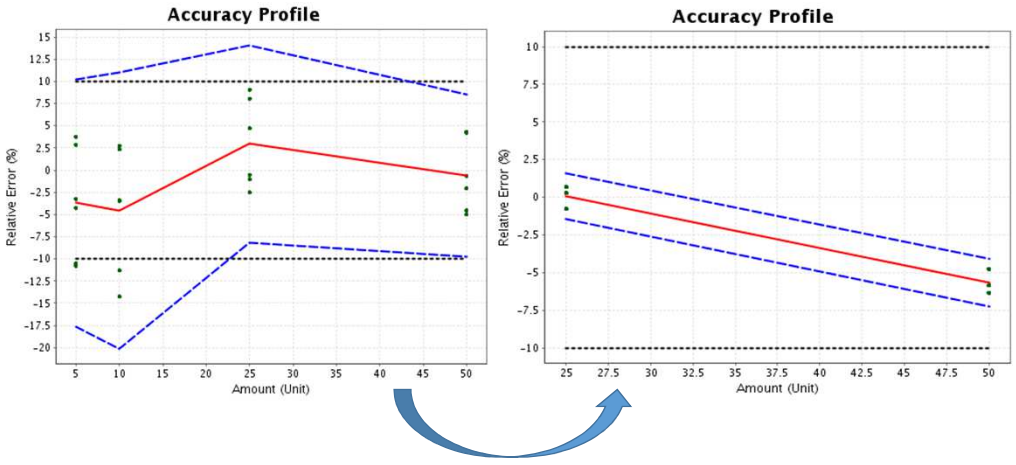


Changing the method



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