Validation

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What is validation?

- The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Qualification vs. validation

- A system must be *qualified* to operate in a *validated* **process**

➢Qualify a system and/or equipment: e.g. you *qualify* an autoclave

➢Validate a process : e.g. you *validate* an autoclaving sterilization process

➢A system must be *qualified* to operate in a *validated* process

3

Qualification vs. validation

4

Qualification

Design Qualification (DQ):

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

5

Qualification

Installation Qualification (IQ):

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

IQ should include:

(a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;

(b) collection and collation of supplier operating and working instructions and maintenance requirements;

(c) calibration requirements;

(d) verification of materials of construction.

6

Qualification

Operational Qualification (OQ):

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

- ❑ This step proceeds after the IQ has been performed.

OQ should include:

(a) tests that have been developed from knowledge of processes, systems and equipment;

(b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.

7

Qualification

- **Performance Qualification (PQ):** The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

- ❑ This step proceeds after the OQ has been performed.

PQ should include:

(a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;

(b) tests to include a condition or set of conditions encompassing upper and lower operating limits.

8

Validation master plan (VMP)

The VMP should contain data on at least the following:

(a) validation policy;

(b) organisational structure of validation activities;

(c) summary of facilities, systems, equipment and processes to be validated;

(d) documentation format: the format to be used for protocols and reports;

(e) planning and scheduling;

(f) change control;

(g) reference to existing documents.

Validation master plan (VMP)

CHANGE CONTROL

- A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes.
- The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Process Validation

Validation and why it is required

- Validation is a component of cGMP.

- FDA has defined process validation as:

  'establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics'

- A new product or an old product manufactured using a modified process or facility can not be sold in USA until the process has been adequately validated.

11

Process validation

The scope of validation

- The manufacturing process must be robust and produce a product with consistent properties.
- This is usually confirmed by manufacturing three full scale production batches under specified conditions.
- In order to minimize cross-contamination between batches, the processes used to clean all equipment in which the product comes into contact must also be validated.

12

Types of validation

- **Prospective validation**: Validation carried out before routine production of products intended for sale.

Prospective validation should include:

(a) short description of the process;

(b) summary of the critical processing steps to be investigated;

(c) list of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with its calibration status;

(d) finished product specifications for release;

(e) list of analytical methods, as appropriate;

(f) proposed in-process controls with acceptance criteria;

(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;

(h) sampling plan;

(i) methods for recording and evaluating results;

(j) functions and responsibilities;

(k) proposed timetable.

13

Types of validation

- **Concurrent validation**: Validation carried out during routine production of products intended for sale.
- In exceptional circumstances it may be acceptable not to complete a validation program before routine production starts.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

14

Types of validation

- **Retrospective validation**: Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

- Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

- For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

15

Types of validation

- **Revalidation**: A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with **change control procedures** do not adversely affect process characteristics and product quality

16

Costs/benefits of validation

- The cost of validation is considerable, with significant resources including personnel and materials being required.
- Inadequate validation may however lead to rejection of, or withdrawal of, legal authorization to manufacture and market the product.
- In other circumstances it may lead to expensive product recalls.
- Other benefits include:
  1. Reduction in process support required
  2. Fewer batch failures
  3. Greater output
  4. Speeding up of marketing authorization

17

Cleaning validation

- As most manufacturing equipment will not be used only in the production of a single product, there is the possibility that, without adequate cleaning procedures, cross-contamination between products may occur.
- Cleaning protocols must therefore be validated to ensure that they are suitable.
- Because equipment can never be 100 % clean, the aim of cleaning procedure is to minimize the possibility of significant cross-contamination between batches of different products.
- A typical specification would be that the contaminant level in the product taken by the patient is not greater than a 1000th of its lower daily therapeutic dose.

18

Cleaning validation

- Once a piece of equipment has been cleaned following a documented procedure, it is analyzed to detect the level of any product residue remaining.

- This may be achieved by:
  A. Swabbing the equipment over a 100 cm^2 area at positions likely to be contaminated and analyzing the swab
  B. Collecting and analyzing rinsings from the final cleaning water.
  C. Producing a placebo batch of the product in the cleaned container.
  D. Visual and tactile inspection

19

Validation of Analytical Procedures

Definition: Testing a method to demonstrate it is suitable for its intended purpose and the results obtained are reliable, accurate and reproducible.

Provides confidence that the method will perform properly under intended conditions.

- Identification tests;
- Quantitative or limit tests for the control of impurities;
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.
- Including assay, Content Uniformity, dissolution, content of presevertives.

20

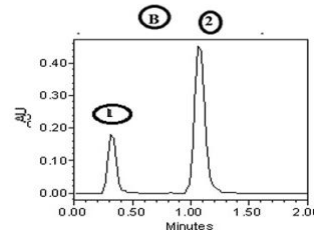
Validation of Analytical Procedures

Characteristics	Type of analytical procedure			
	ID	Impurities		Assay
		limit	quantitative	
Specificity	+	+	+	+
Accuracy			+	+
Precision				
Repeatability			+	+
Intermediate precision			+	+
Linearity/Range			+	+
Limit of detection(LOD)		+	+	
Limit of quantitation(LOQ)			+	

21

Specificity

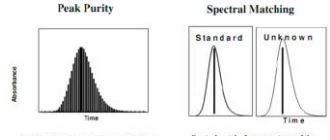
- Specificity is the ability to measure specifically the analyte in the presence of other components which may be expected to be present.
- Typically these might include impurities, degradants, matrix, etc.
- Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).



22

Specificity

- Blank solution - to show no interference
- Placebo - to demonstrate the lack of interference from excipients
- Spiked samples - to show that all known related substances are resolved from each other
- Stressed sample of about 10 to 20% degradation is used to demonstrate the resolution between degradants and the analyte of interest
  - Check peak purity of drug substance by photodiode array detector (PDA)
- Representative chromatograms should be provided



23

LOD / LOQ

- **LOD :**The limit of detection of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.
- **LOQ :** The limit of quantitation of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

Parameter	*Value*	
	Lisinopril	*HCT*
LOQ, µg /mL	0.155	0.025
LOD, µg /mL	0.039	0.012
RSD of peak areas for LOQ (n= 6)	2.001	3.343
RSD of retention times for LOQ (n= 6)	0.050	0.073
s/N for LOQ	18.23	14.25
s/N for LOD	4.03	7.98

24

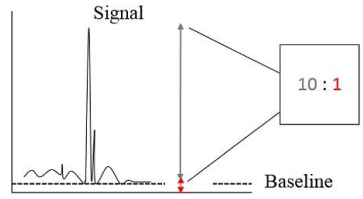
LOD / LOQ

- Visual evaluation (non-instrumental method)
- signal to noise ratio: LOD 3:1 , LOQ 10:1
- standard deviation of the response and the slope of the calibration curve at levels approximating the LOD /LOQ

σ = $DL = \frac{3.3\sigma}{S}$ on of the response $QL = \frac{10\sigma}{S}$

S = the slope of the calibration curve

should be validated by analysis of samples at the limits.



25

LOD / LOQ

- LOD: below the reporting threshold
- LOQ: at or below the specified limit

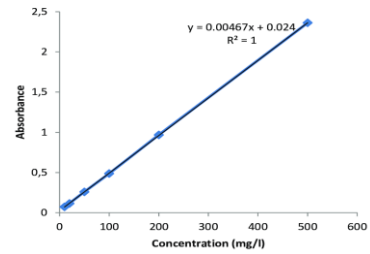
Not required for assay/dissolution methods.

- Applicant should provide
  - the method of determination
  - the limits,
  - chromotograms

26

Linearity / Range

- The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.
- The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.
- Minimum 5 concentrations



Linearity / Range

- Assay : 80-120% of the test concentration
- E.g Strength 200 mg. Linearity:160-240 mg
- Content Uniformity: 70-130% of the test concentration
- Dissolution: ±20% of limits; in immediate release limits cover from 20% to 90% label claim (l.c). (controlled release), linearity should cover 0-110% of l.c.
- Impurities: LOQ to 120% of shelf life limit(at least 120% of the proposed specification limits for impurities and degradation products.)
- Assay/Purity by a single method: LOQ of the impurities to 120% of assay limit

28

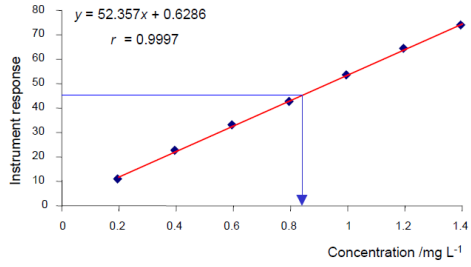
Linearity / Range

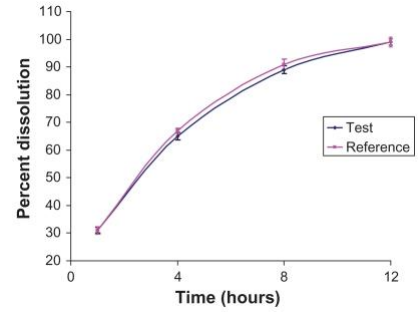
Correlation coefficient (r)

Assay: r ≥ 0.999

Impurities: r ≥ 0.99

y-Intercept and slope should be indicated together with plot of the data





29

Accuracy

- Expresses the closeness of test results obtained by that procedure to the true value= trueness
  - the value accepted as a conventional true value, or
  - an accepted reference value and the value found
- accuracy should be established across the specified range of the analytical procedure

Sample	Injected concentration (µg/mL)	Concentration found (µg/mL)	Accuracy (%)
Naproxen	32.0	33.3	104.2
	36.0	35.8	99.5
	40.0	39.7	99.4
	44.0	44.3	100.7
	48.0	47.9	99.7
Rabeprazole sodium	16	15.7	98.1
	18	18.1	100.3
	20	20.1	100.6
	22	21.8	99.1
	24	23.9	99.4

30

Accuracy

$$\%RSD = \left(\frac{SD}{mean}\right) \times 100$$

Assay

API: against a Reference Standard of known purity, or via an alternate method of known accuracy; analysis in triplicate.

FPP(Finished Pharmaceutical Product): placebo/drug product spiked with known quantity of API, in triplicate at each level (80, 100 and 120% of label claim) is recommended.

Report recovery (mean result and RSD): 98.0-102.0%

ICH Q2 states: accuracy may be inferred once precision, linearity and specificity have been established. (Demonstration preferred).

31

Accuracy

Impurities:

API/FPP spiked with known amounts of impurities

Recommendations:

Across the range of LOQ-150% of the target concentration (shelf life limit), 3-5 concentrations, in triplicate each. (LOQ, 50%, 100%, 150%)

Percent recovery: in general, within 80-120%, depends on the level of limit

% Drug Solution	mg Obtained	% Recovery
50%	50.150	100.30
	49.255	99.10
	49.956	99.71
100%	100.136	99.94
	99.256	99.26
	99.957	99.76
150%	150.375	100.05
	148.242	99.16
	148.764	99.18

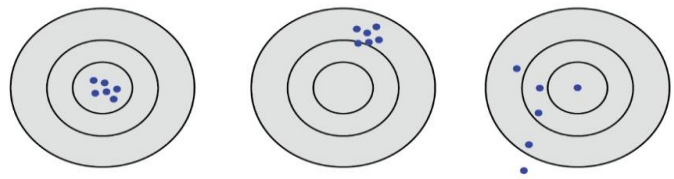
32

Precision

- **Precision** of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of test results obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.
- **(degree of agreement among individual test results).**
- It should be measured by the scatter of individual results from the mean and expressed as the relative standard deviation (RSD).
- May be considered at three levels
  - Repeatability
  - intermediate precision (ruggedness)
  - reproducibility.

33

Precision



High Accuracy High Precision | Low Accuracy High Precision | Low Accuracy Low Precision

Sample	Injected concentration (µg/mL)	Intra-day (n=3)		Inter-day (n=3)	
		Concentration found (µg/mL)	Precision (% RSD)	Concentration found (µg/mL)	Precision (% RSD)
Naproxen	10.0	10.4	1.3	10.3	1.3
	20.0	19.7	1.9	20.2	0.4
	40.0	40.6	0.4	38.9	0.1
Rabeprazole sodium	5.1	5.3	1.5	4.9	0.6
	10.1	10.6	0.2	10.2	0.9
	20.2	19.9	1.2	20.0	0.7

34

Precision

- **Repeatability** (method precision)
  - Multiple measurements of a sample by the same analyst
  - A minimum of 6 determinations at the test concentration (6 times of a single batch), or
  - 3 levels (80%, 100%, 120%) , 3 repetitions each

  Recommendation:
  - For Assay: RSD ≤ 2.0%
  - For individual impurity above 0.05%, in general, RSD ≤ 10%

35

Precision

- Intermediate precision(ruggedness)
  - Test a sample on multiple days, analysts, equipments
  - RSD should be the same requirement as method precision
- Reproducibility (inter-laboratory trial)
  - Not requested in the submission
  - Need to be considered for method transfer

36

Precision

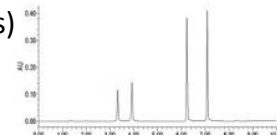
	Repeatability Condition	Intermediate Precision Condition	Reproducibility Condition
Laboratory	Same	Same	Different
Operator	Same	Different	Different
Apparatus	Same	Same a	Different
Time between Tests	Short b	Multiple Days	Not Specified

a This situation can be different instruments meeting the same design requirement.
b Standard test method dependent, typically does not exceed one day

37

Robustness

- The method's capability to remain unaffected by small but deliberate variations in method parameters (for HPLC)
  - Influence of variations of pH in a mobile phase
  - Influence of variations in mobile phase composition
  - Different columns (different lots and/or suppliers)
  - Temperature
  - Flow rate



- *Establish the System suitability parameters*
- (Resolution, Retention time, Pressure, Column efficiency, Repeatability ,Plate Number ,Tailing factor, Signal-to-noise ratio)
- If robustness indicates a limitation, this must be clearly stated in the method

38