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Protection des consommateurs

BPL e Sistema Computadorizado

Rio de Janeiro, 27.09.2018

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Programação do dia 27.09.2018

09:00 - 10:30 Introdução e termos especificos
10:30 - 11:00 Intervalo
11:00 - 12:00 Conceito global de validação

12:00 - 13:30 Almoço

13:30 - 14:30 Exemplo de validação “Spreadsheet”
14:30 - 15:00 Intervalo
15:00 - 17:00 Inspeção de systema informatizado, estudo de casos. Discussão.

Content

GLP requirements

Specific terms

Validation and change control

Operational phase

Development and validation of Spreadsheet

Inspecting computerised systems

Legal requirements : OECD GLP Principles

Principal requirements :

Management should … establish procedures to ensure that **computerised systems** are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.

SOPs should be available for … validation, operation, maintenance, security, change control and back-up of **computerised systems**

OECD Interpretations of the legal requirements

Consensus Document Nb 10 (retired)

The Application of the Principles of GLP to Computerised Systems (1995)

Advisory Document Nb 17

Application of GLP Principles to Computerised Systems (2016)

The following Advisory Doc. replaces the 1995 consensus document . It retains all of the key text from the original Consensus Doc. Nb 10, but includes new text to reflect the current state-of-the art in this field :

> Life cycle concept
> User requirement specifications (URS)
> Risk management approach

Swiss Interpretations of the legal requirements

(AGIT) Guidelines on computerised systems

https://www.anmeldestelle.admin.ch/chem/en/home/themen/gute-laborpraxis/agit.html

> Validation of Computerised Systems
> Guidelines for the Acquisition and Processing of Electronic Raw Data
> Guidelines for the Archiving of Electronic Raw Data
> Guidelines for the Change Management and Risk Assessment
> Management of Electronic SOPs
> Development and Validation of Spreadsheets
> Guidelines for Collaboration with external IT Service Providers

All Guidelines are compliant with OECD Advisory Doc. Nb 17

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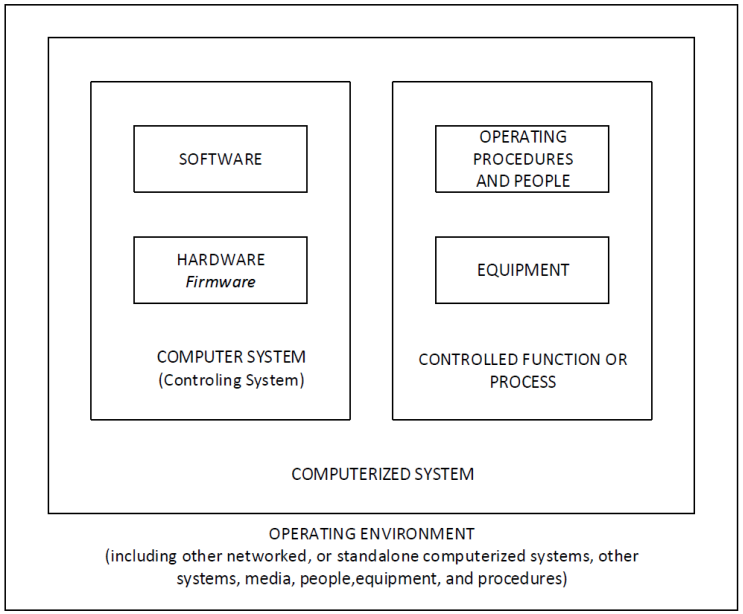
Computerised system

Process or operation integrated with a computer system (hardware and software) and performed by trained personnel



Computerised System includes controlled equipment and trained personnel

Validation

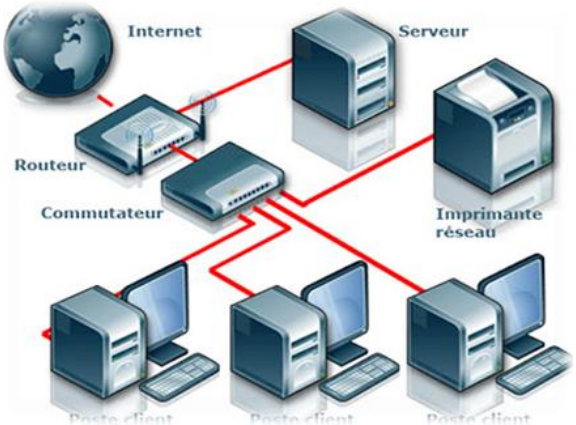
Definition

Action of proving that a process leads to the expected results.
Validation of a computerised system requires ensuring and demonstrating the fitness for its purpose / that the system meets its pre-determined specifications.

Remark

Validation is used as a global term for all computerised systems and also as a specific procedure for some systems

Great variety of computerised systems



GLP Principle
.. **(all) computerised systems should be validated** …. ??

Categories of Computerised system

Category A	**Exempted Systems**
Definition	No calibration function Framework/layered software
Examples	Calculator, microscope, photo or video camera, standard office PC, Microwave, etc. Operating system, network software, security software (virus check, firewall), application software, data base software
Action	None
Documentation	Inventory list, system description

Categories of Computerised system

Category B	**Simple Computerised Systems**
Definition	Small part of software Restricted customisation
Examples	pH-meter, titration processor, colorimeter, thermo hygrograph, balance, particle sizer, UV/VIS spectrometer, liquid scintillation counter, TLC analyser, image analyser, polarimeter, etc.
Action	System SOPs (for use, maintenance, function control test) ; Calibration ; Function control test *> Qualification in Doc. 17*
Documentation	Logbook / change control log file User training

Categories of Computerised system

Category C	**Complex Computerised Systems**
Definition	Extended amount of functionality software Extended customisation
Examples	LIMS, automated sample processing systems, liquid chromatograph (LC, HPLC), gas chromatograph (GC) including auto sampler and detection systems.
Action	Validation
Documentation	User requirement specifications ; Risk assessment ; Validation plan ; Validation raw data ; Validation report ; System description ; Logbook / change control log file ; System SOP's (for use, maintenance, function control test) ; User training

Specific systems

Commercial off-the-shelf products (COTS)

COTS are computerised system available in multiple and identical copies (e.g. chromatograph)

COTS require appropriate validation depending of complexity and customisation.

Customised system

System developped for a specific use by a test facility

Spreadsheets

Spreadsheets (e.g. Excel) with self-written equations and macros needs :

- to be validated, or
- to be checked in case of single use

Change control

Definition

Ongoing evaluation and documentation of system operations and changes to determine whether a validation process is necessary following any changes to the computerised system.

Any changes to a computerised system should be made in a controlled manner and in accordance with written change control procedures (approval, documentation, testing, release).

Change management is the global process of change controls

Types of changes

Administrative, maintenance, emergency or intended changes

Change control

Types of change	Example	Action required
Administrative	New responsibility	Update documentation
Maintenance	Replacement of attrition parts	Documentation in log book Function control test
Emergency	System failure	Immediate repair Function control test Retrospective RA
Intended	Planned upgrade or modification	Risk assessment (URS affected) Low impact -> control test **High impact -> validation of affected URS** Documentation

Life cycle

Definition

All phases from specification, purchase, design, development and testing, implementation, operation and retirement

Life cycle phases

Project phase – operational phase – retirement phase

User requirement specification (URS)

Definition

The users formally compile all requirements in a document called user requirement specifications. These user requirements contain scientific, business, regulatory, security, performance and quality aspects of the future system and should cover all GLP-relevant functions of a system.

URS is part of the project phase of the computerised system life cycle

Application

The URS serve as the basis to establish the extend of the qualification (OQ, PQ), following a risk assessment of each user requirement

Risk assessment, Risk management

Definition

Risk assessment should be used to develop an adequate validation strategy and to scale the validation efforts. The validation effort should be driven by the intended use of the system and potential risks to data quality and data integrity. The outcome of the risk assessment process should result in the design of appropriate validation activities

Example URS and Risk assessment

The new version of the software has an improved auto integration functionality (new algorithm). Several user requirements are affected and should be tested.

Operation	User Requirement	User requirement affected	Test required	Justification
	...			
Data processing and evaluation				
4.1	Manual integration function, i.e. set start and end of fraction on graph and on time event table.	No		
4.2	Definition of BG area.	No		
4.3	Smoothing of signal, i.e. 2-10 point smoothing.	Yes	Yes	
4.4	Auto integration based on slope and treshold.	Yes	Yes	
4.5	Batch re-processing of integration based on defined integration methods	Yes	Yes	
	...			

If none of the affected user requirements needs to be tested, this change is considered as a low impact change. As soon as testing of one or more user requirements is required the change is considered as a medium or high impact change. The difference between medium and high impact is the extent of testing necessary.

Electronic Record / Raw Data

Definition

Any combination of text, graphics, data, .. created, maintained, archived, .. by a computer system.

E-Raw data : Original records generated by means of computerised systems and stored on digital media (archiving time as for paper raw data)

Meta-data contain the attributes of the measured values (e.g. study number, time, sample identification) and technical properties (e.g. table relationships).

Proprietary form: electronic file format which needs a dedicated software to be read and processed (opposite to human readable form)

Personnel

Role and responsibilities

Test facility management, study director and quality assurance personnel have similar responsibilities with computerised systems as with other apparatus. Personnel operating a computerised system should have appropriate qualification.

IT personnel : Personnel involved in the purchase, installation and maintenance of computerised systems (hardware, software, backups)

During validation, roles and responsibilities should be defined and controlled via system access privileges

- System owner
- Validation director

Supplier / Service provider

In the GLP environment, collaborations with external IT service providers are increasingly used in data capture, processing, storage and archiving, as well as IT infrastructure.

SLA

A service level agreement (SLA) shall be concluded with external IT service providers. SLA should cover:

> Role and responsibilities
> Security and access control
> GLP training requirements and personnel records
> Audits by TF QA and GLP monitoring authorities

Documentation

Inventory

An up-to-date listing (inventory) of all GLP-relevant computerised systems and their functionality should be maintained. The inventory should contain the validation status, model or version as relevant, and business process owner and IT system owner (persons who have responsibility or accountability for the system).

Documentation for each computerised systems

System components (hardware, software), operation, maintenance, change control procedure
back-up and business continuity procedures, archiving and retrival of electronic data, etc.

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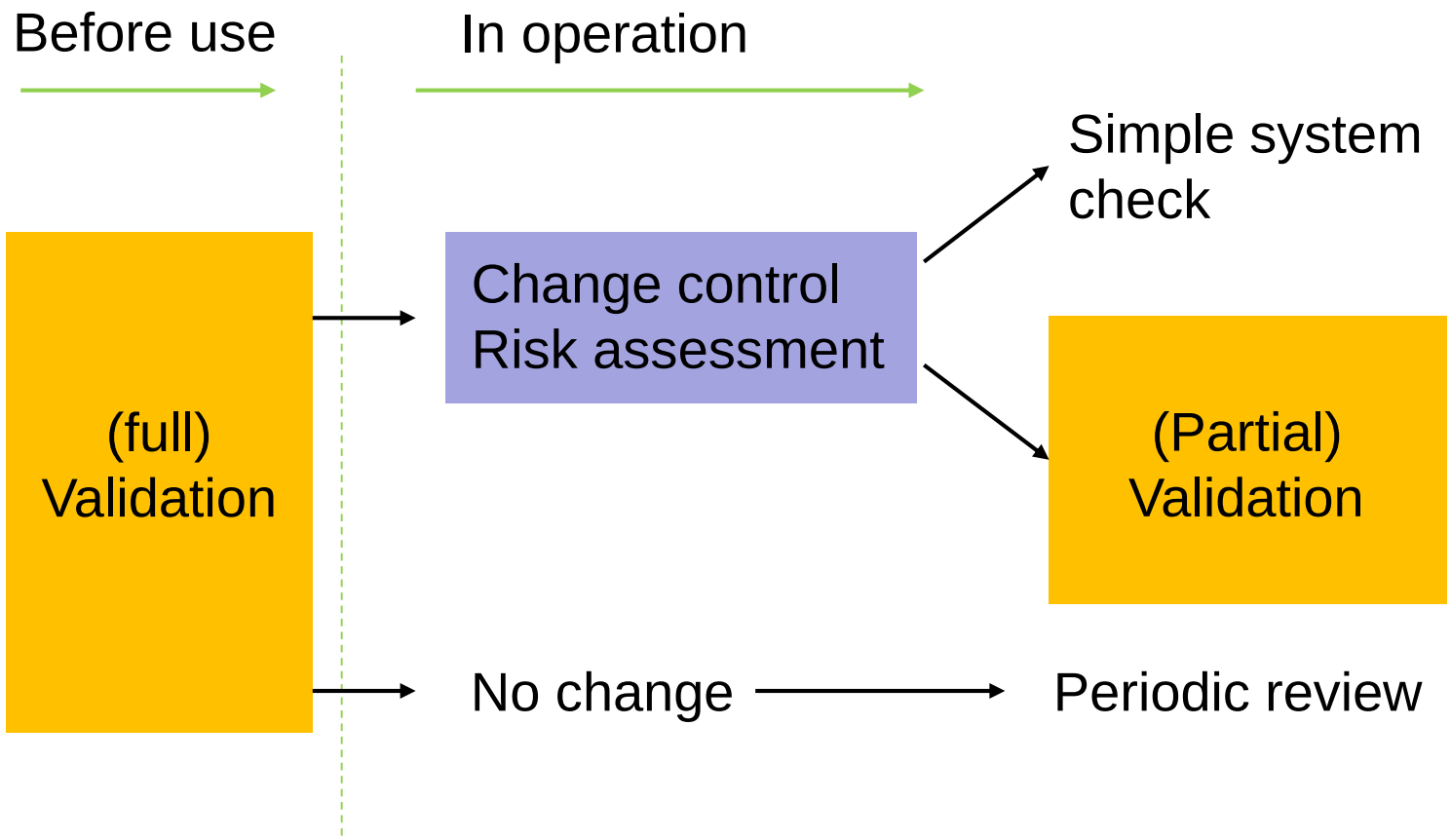
Global validation concept



Validation

- A computerised system should be validated before its operational use (project phase of the life cycle). Following a change with possible impact on the validated status, the modified functions of the system should be validated (operation phase)
- Validation could be organised as a GLP study
  > validation plan
  > validation data
  > validation report

Validation

- The amount of validation depends on the complexity of the computerised system :
  COTS (HPLC, GC) → relative simple
  Customised system (LIMS, Excel with macros) → complex
- Change control
  Impact of any change on the validated system should be assessed on a risk base. Decision should be taken to validate or not the impacted functions of the system.

Validation plan (I)

- Validation plan should mention URS and existing system qualifications (should be available in the test facility)
  > URS should be established for each computerised system also for COTs
  > IQ, OQ may be provided by system supplier. OQ must be reviewed by system owner to evaluate if additional test scripts are necessary to cover all important functions
- An index of all documentation relating to the computerised system, including but not limited to SOPs, user developed documentation, and vendor/provider developed documentation should be provided.

Validation plan (II)

- System description (hardware and software version)
- Responsibilities
  System owner, validation director/officer, IT personnel, QAU, management
- Tests to be realised, with acceptance criteria (PQ)
- The user requirements serve as the basis to define the tests and the acceptance criteria. They should cover the overall business use (use cases) of the system in the daily routine.
- Guidance should be provided for the change control during validation

Validation plan (III)

- The validation plan concerning the first (full) validation of the system is called **master** validation plan
  > should mention all URS
  > should mention IQ and OQ
- The validation plan following a system change :
  > should mention the master validation plan
  > should mention the system change(s)
  > should mention the list of impacted URS and contain a risk assessment analysis of each impact (test required yes/no)

Data transfer

- Exchange of electronic data between an equipment (e.g. HPLC) and a centralised data management system (LIMS) should be validated
- Depending of the system organisation, the data transfer may be validated with the equipment or with the LIMS system (influence on validation plan)

Validation data (raw data)

- Validation data can contain manual records, print outs or display capture
- Data should clearly indicate if the test result was within specification according to study plan

Validation report

- Report should contain a description of the tested system (inclusive software version)
- Purpose of the validation
- Eventually, reference to URS, IQ, OQ
- Result of tests and deviations
- GLP and QA statement (optional)
- Release approval
- Personnel responsibilities and signatures

Change control and risk assessment

- After release of the computerised system a change management process is needed to ensure the continuous validation of the system
- Change control required a controlled process to monitor and document all changes of the released system.
- Roles and responsibilities for accessing and approving changes should be clearly defined (e.g. updates in operating system)
- Changes should be evaluated with regard to their impact (risk assessment) on the validation status and appropriate measure should be taken to keep the system in a validated state.

Implementation of change and validation status

- For changes with high impact the computerised system will no longer be valid for productive use as of change execution
- Change period should be documented in system logbook (with reference to validation documentation)

Periodic review

- Computerised systems should be periodically reviewed to confirm that they remain in a validated state, are compliant with GLP and continue to meet stated performance criteria (e.g. reliability, responsiveness, capacity etc.).
- Review may include deviation records, incidents, upgrade history, performance, reliability, etc.
- Computerised system of less complexity may be excluded from the review if justified based on risk.
- A periodic user review is recommended

System retirement

At the end of the system life cycle, the system should be retired. The retirement should be performed according to a formal system retirement plan, risk based and documented in a report approved by the test facility management or the system owner. The entire system documentation (log books, system manuals etc. in paper or electronic form) and if applicable the software applications should be archived. The retirement of the system may have an impact on the accessibility and readability of the archived electronic raw data generated by the system.

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Manual Data Entry and printouts

Manual Data Entry

Data entered manually into electronic system is a critical issue.

> Check of accuracy by a second operator (should be documented), or

> automated check on entered data (should be validated)

Printouts

If raw data is defined as data on paper, all electronic data, including meta data (study nb, sample id, time) and data changes, should be printed

Electronic (raw) data and data storage

- When raw data are stored electronically, requirements for back-up and archiving purposes should be defined.
- Stored data should be secured by both physical and electronic means against loss, damage and/or alteration
- Hardware and software system changes must allow continued access to, and retention of the data without any risk to data integrity
- Written procedures should be available on storage, protection and readability of data

Processed data

- Acquired electronic raw data, (such as intensity values, correlated with time or wavelength and generated by chromatography), need further processing to obtain usable results
- In contrast to raw data, processing parameters may be changed during data evaluation.
- Only the processed data that are finally used and the corresponding process should be retained and archived in addition to the electronic raw data.

Audit trails

- An audit trail provides documentary evidence of activities that have affected the content or meaning of a record at a specific time point. Audit trails need to be available and convertible to a human readable form.
- Any personnel involved in a study should not be authorised to change audit trail settings

Electronic signature

- Electronic records may be signed electronically
- Electronic signature should
  > have the same legal consequence as a hand-written signature (no change in document)
  > be permanently linked to the respective record
  > include time and date of application
  > allow identification of the signatory
- Test facility should have an electronic signature policy (which documents, authorised persons, etc)

Physical security and data integrity

- Documented security procedures authorised by test facility management should be in place for the protection of hardware, software and data from corruption or unauthorised modification, or loss.
- Suitable control methods for preventing unauthorised physical access to the system should be in place
- For equipment not held within specific “computer rooms” (e.g. personal computers and terminals), there should be access controls to the area where the hardware is located

Archiving

- It is important that electronic data is stored with the same levels of access control, indexing and expedient “retrieval” as non-electronic data.
- Viewing electronic records without the possibility of alteration or deletion of the archived electronic records or replicating within a computerised system or to another computerised system does not constitute “retrieval” of records.
- Electronic archiving should be validated appropriately. Relevant hosting systems and data formats should be evaluated regarding accessibility, readability and influences on data integrity during the archiving period

Archiving

- Consideration may have to be given to archiving electronic data in an open format that is independent from proprietary file format e.g. from an instrument manufacturer.
- In the study report, the study director should identify all GLP-relevant electronic data which are subject to electronic archiving and the location of the electronic archive.

Business continuity and Disaster recovery

- Provisions should be made to ensure the continuity of support for computerised systems which are used for GLP-relevant processes in the event of a system breakdown . Procedures should be in place (e.g. record on paper form)
- if the manually recorded data is subsequently entered into the computer it should be clearly identified as such. The manually recorded raw data should be retained as the original record and archived.
- Procedures should depend on the criticality of the system

Content

Definition of terms

Validation and change control

Operational phase

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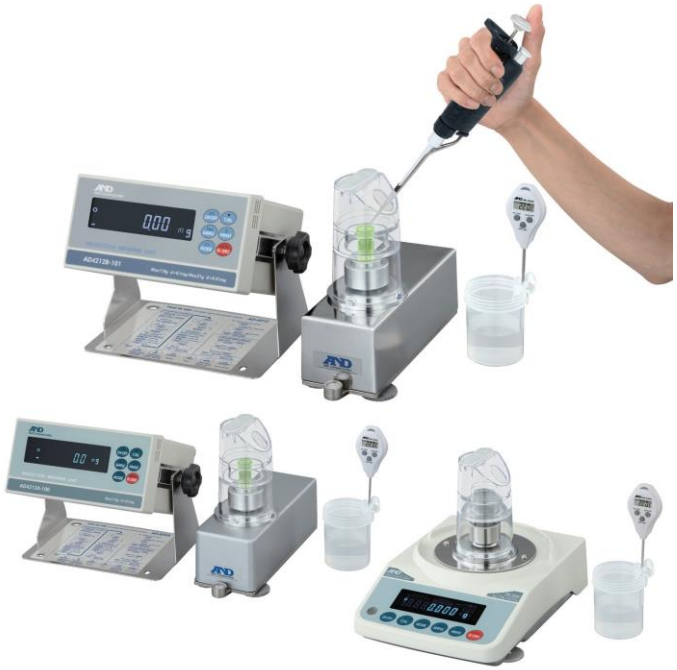
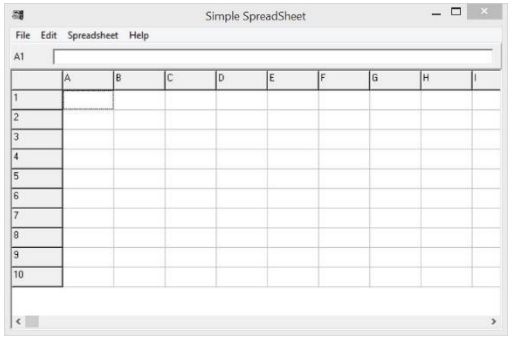
Inspecting computerised systems

Spreadsheet

- Spreadsheet (e.g. Excel) are widely used for the storage, processing and reporting of data in a GLP environment. [with raw data or copied set of raw data]
- They should be developed, validated, operated, maintained, retired and archived in accordance with GLP principles applicable to computerized system.
- Not concerned:
  > tabulating spreadsheets that do not contain raw data
  > spreadsheets employed as single-use calculation sheets

Example : Spreadsheet for gravimetric pipette control





Spreadsheet for gravimetric pipette control

User Requirements

The users should define what they expect the spreadsheet to do, which calculations have to be performed, the layout, etc. Examples:

URS-1. The spreadsheet should be applicable for volumes from 0.01 to 10 mL
URS-2. The spreadsheet should only accept a sample number of 10
URS-3. The spreadsheet should calculate the mean, standard deviation (SD) and relative SD (RSD=(SD/average)x100%) of the 10 samples
URS-4. The spreadsheet should use the density of water between 20°C and 25°C in steps of 1°C

Spreadsheet for gravimetric pipette control

User Requirements

URS-5. The Inventory Number of the pipette should be visible on the screen and on the print-out.
URS-6. The spreadsheet should indicate whether the accuracy and RSD fulfil the acceptance criteria according to the SOP
URS-7. The spreadsheet input should only allow numerical values for the nominal volume of the pipette, sample weight and temperature

Spreadsheet for gravimetric pipette control

Requirements concerning security, protection and GLP compliance should also be defined. Examples:

URS-21. The calculations in the spreadsheet should be protected against unauthorised modifications
URS-22. After completion of the measurement, the spreadsheet should be initialled and dated electronically by the user
URS-23. Making changes to the spreadsheet (modification/deletion) after signing off (initials/date) should not be possible
URS-24. The spreadsheet template and completed spreadsheets should be retained in a secure location in an electronic form with access control

Spreadsheet : Development

Importance of Spreadsheet design

> Reduce the number of errors during programming,
> Make it easier to maintain, adapt or further develop the spreadsheet and
> Make it easier to verify the function during validation.

Example :

The spreadsheet is divided into an area where data input occurs, an area where the results are calculated and presented and an area containing constants and criteria

	A	B	C	D	E	F	G	H	I	J	K	L
1	Pipette (Inventory Number)	AQ77		Result				Decision criteria				
2	Nominal Value (ml)	10.00			g	ml		Max Delta	%	1.0	according to SOP	
3				mean	10.01	10.032		RSD	%	1.0	according to SOP	
4	Measurements			standard dev.	0.02	0.02						
5	Sample	g		RSD, %	0.2	0.2		Nominal Value	ml	10.00	calculated	
6	1	10.0600						Max Delta	ml	0.10	calculated	
7	2	9.9999		Density @ 23 °C is	0.997538							
8	3	10.0010						Temperature	Density			
9	4	9.9996		Accuracy	ok			deg. C	g/ml			
10	5	10.0000		RSD	ok			20	0.998203			
11	6	10.0230						21	0.997992			
12	7	9.9919						22	0.99777			
13	8	10.0002						23	0.997538			
14	9	9.9999						24	0.997296			
15	10	9.9998						25	0.997044			
16				Date/Time	Operator							
17	Temperature (°C)	23						http://faculty.cbu.ca/chowley/chem202/dh20vstemp.htm				
18	Enter/Save							From the Handbook of Chemistry and Physics, 62nd ed.				
19								Version 1.01				
20												
21												
22												
23												
24												

Spreadsheet : Testing

Testing during development

> The developer tests whether the spreadsheet fulfils the URS
> The content of cells is controlled

Release for qualification

> Documentation (user guide) should be complete
> From this stage onwards, version control of the spreadsheet is highly recommended.

Spreadsheet : Qualification process

Installation qualification (IQ)

Special attention should be given to:

> The spreadsheet can be run on different computers

> The spreadsheet can be installed and run using different software versions.

Operational qualification (OQ)

Not necessary to repeat all tests (see development testing)

Choose input values that lead to unacceptable or impossible results. Example :

URS-7

Test : Enter “q” as weight in the sample 1 field.

Test result : The error message “Please enter a weight in grams!” appears.

Spreadsheet : Qualification process

Performance qualification (PQ)

> Test with selected input data to verify all possible and all special cases

> Test with real data

URS-3, URS-6

Test:	Enter the following values for samples 1–10: 9.95, 9.95, 9.99, 9.99, 10, 10, 10.05, 10.05, 10.4, 10.4
Test result :	Results: mean 10.078 g, SD 0.173, RSD % 1.717, Accuracy ok, RSD out of spec

Spreadsheet : Release

- Following successful completion of qualification the system is released for use by test facility management.
- This responsibility may also be delegated to the system owner

Spreadsheet : Change management

Any changes to the spreadsheet should be handled using systematic change management procedures. New version number should be used following any change

- Certain changes to a spreadsheet may not necessitate additional testing.
  Example: adaptation of acceptance criteria (as specified in equipment SOP)
- Other changes may require additional testing

Spreadsheet : Qualification or validation ?

- The qualification process corresponds to the “full” validation of the computerised system
- Additional testing following a major change leads to a “partial” validation of the system

Spreadsheet : How to document the validation

The concept of validation plan / validation raw data / validation report facilitates the the overview and the link between the qualification documents.

Validation plan

> Refers to URS, IQ, OQ (attached or linked documents)
> Definition of responsibilities
> Tests and expected results for PQ (following OQ analysis)

Validation report

> System and document overview
> Test results and eventual URS adaptation
> Change management procedure
> System release

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Inspection preparation

- Request IT documents
  > Ask for the list of computerised systems (inventory), with validation status, including customised systems (Excel spreadsheet)
  > Eventually ask for specific SOPs on validation
  > Eventually ask for a list of IT validations (since the last inspection)
- Get understanding of the IT organisation
  > External support ?
  > Archiving of electronic raw data ?
  > Localisation of computerised systems ?
  > Server room ?

Inspection planning

- Plan time slots for
  > Interviews (IT, TFM, QA, users)
  > Inspection of IT infrastructure (server room, archive)
  > Inspection of computerised system(s)
- Choose a computerised system to be inspected
  > Relevant for the test facility
  > Used in a study that will be audited during the inspection

During the inspection

- Discuss with IT responsible
  > Validation concept in the test facility
  > Review list of computerised systems and validation status
  > Check use of external IT support and availability of SLA
- Interview TFM, QA, Users
  > Check / understand interactions between actors
- Check documentation
  > Personal records (qualification, training)
  > Global validation strategy
  > SOP on validation procedure and responsibilities
  > SOP on management and archiving of electronic data

During the inspection

Inspect one computerised system :

> Check logbook
> Verify change control records and decisions concerning validation
> Choose one validation “study” (out of the archive)
> Check availability of IQ, OQ documents
> Check URS, Risk assessment, tests and results
> Verify decision concerning system “release”
> Check security aspects (adequate location, electrical supply, Back-up strategy)
> In case of electronic raw data (no paper) : check electronic archiving, access to archived data, policy to ensure data readability after system upgrades.

Case study 1

Stand alone chromatographic equipment (HPLC, GC, ..)

- The system is “validated” once a year with a standard PQ / system suitability test SST (reference substance : determination of repeatability, linearity, tailing, ..). No user requirements.
  IQ, OQ are archived

Is it OK ?

Case study 1

Stand alone chromatographic equipment (HPLC, GC, ..)

- The user considers that the system specifications cover his needs (functionalities, printout format, etc.) ?
- Analysis is performed with a reference substance ?
- SST is run before / during the measure ?
- A change control concept is in place (system validation in case of change with high impact) ?

Case study 1

Stand alone chromatographic equipment (HPLC, GC, ..)

- Ok with simplified validation strategy

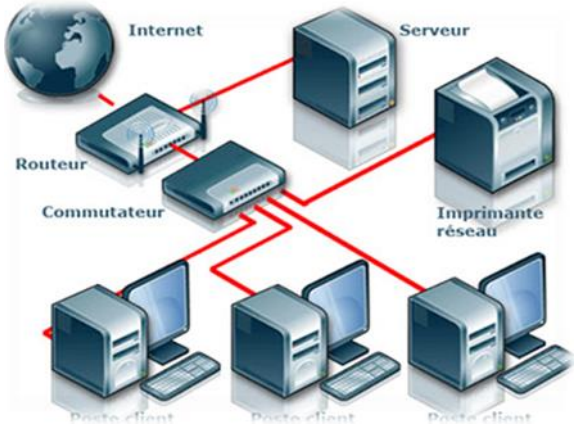
But :

- PQ should not be a “simple” SST. Consider if other functionalities need to be tested (e.g. communication PC to equipment, information on printout (study and sample ID), Integrity of data in case of summary table produced by the system)
- In case of validation following an important change, PQ should be adapted to the impacted functionalities of the system

Case study 2

LIMS

- Validation of LIMS can be difficult to be inspected. An explicit validation plan with a good description of user / system requirements is necessary.



How to make sure that test scripts cover all expected uses / functions of the system ?

Case study 2

LIMS

- Ask support of validation director/officier
- Check validation of data transfer (equipment to server)
- Ckeck relation study design and data allocation
- …..

??

Questions

Thank you for your attention