

PERFECT CONSULTANTS

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6 GOLDEN RULES OF VALIDATION

1.0 DRAFT A PERFECT PLAN FOR VALIDATIONS

Normally, entire validation activities in any organization is performed using Master Validation Program. If MVP is perfect, success in validation is assured. Exercise following precautions in drafting MVP

Avoid Critical Miss Outs:

Many of MVP,s have critical miss outs. Very often atypical MVP includes Equipment validation, Process validation, HVAC & Water system validations and Method validation but misses out Computer System validation. Some MVP,s even do not provide scope for revalidation. Retrospective validations for the existing system and equipments are also missed out many times.

Specify frequency of Validation/ Revalidations.

Master validation Plan shall provide clear statement of frequency of Validation / Revalidation so as to ensure that systems are maintained in validated state through out their life cycle.

Provide detailed information on validation team

MVP shall clearly state Name/ Designation of validation team members and their individual and joint responsibilities.

Cover all the critical validation activities

The validation activities require the following steps

- Drafting validation protocol
- Approval of the protocol.
- Experimentation and observation as per the protocol.
- Recording of results
- Interpretation of results
- Comparison of results with acceptance criteria.
- Remarks
- Final validation report(validation summary and recommendation)

Final certification and approval by all team members

Most of the Master Validation Plan does define validation procedure but the same is found incomplete and out of sequence.

Provide Cover statement on out of validation equipments

MVP shall provide clear guidelines on prohibition repair and revalidation of out of validation equipments has been found missing in Master Validation plan. Out of validation equipment shall be immediately withdrawn from the process chain .Further the products manufactured using the same shall be checked for unnoticed errors.

2.0 DRAFT THE MOST STANDARD PROTOCOL

Drafting a protocol for validation is not a simple task. The protocol should be designed by the validation team and verified with the supplier of machine.

Most common error in drafting protocol is

- a) Protocol is not relevant.
- b) Protocol does not cover critical feature of design, operation or performance.
- c) Acceptance Criteria not well defined.
- d) Provision for statistical analysis is not present.
- e) Validation report not available
- f) Instructions for recording the data not provided.
- g) No details on Annual validation activities.
- h) No details on labeling of equipments on actual date of validation and due ate for validation.
- i) No details on archiving of validation studies and data.

The validation plan for the different systems may be drafted as per follows:

Process validation:

- Approval of protocol
- Checking suitability of Raw materials
- Checking suitability of machines
- Identification of critical process parameters
- Defining limits of critical process parameters.
- Recording actual values in Critical Process Parameters
- Evaluating compliance with Critical Process Parameters
- Identifying Critical Quality Attributes of the finished product
- Recording actual values of Central Quality Attributes
- Evaluating compliance with Central Quality Attributes
- Repeating the whole process for 2 more consecutive batches
- Comparing consistency of the results
- Validation report
- Approval of report

Method Validation:

Accuracy checks
Precision checks
Linearity checks
Specificity checks
Robustness checks
Solution stability checks
L.O.D
L. O. Q

Water System validation:

Water System Validation involves D.Q., I. Q, O.Q, P.Q. of the system. It is performed on the entire system. DQ, IQ, OQ confirm to normal machine validation.

However P.Q involves-

Identification of sampling locations for D. M plant, R.O plant, water storage tanks and final delivery points



Testing for Chemical and Microbial Attributes



Comparing the results with predefined acceptance criteria for each sampling point



Repeating the sampling and analysis daily for 30 days followed by Weekly for 3 months and monthly for 1 year.

HVAC Validation:

It involves D.Q, I.Q, O.Q, & P.Q of the system.

D.Q, I.Q, and O.Q usually confirms normal machine validation.

However P.Q involves identification of sampling points so as to cover diffuser, riser, exhaust points, processing area and corners

P.Q also specifies types of the physical and microbial tests to be conducted at all identical locations

Normally following tests are performed

1. Temperature
2. Humidity
3. Particle Count
4. Air Velocity
5. Differential Air pressure
6. Microbial Count
7. Air Changes

8. Filter Integrity

All these tests are performed duly validated test equipments. The results are recorded and evaluated against predefined standards. The test procedure is performed under static and dynamic conditions. The frequency of test procedure is defined before commissioning the area and after that normally validation is continued over 12 months.

Computer system validation

Normally this involves D.Q, I.Q, and O.Q like other machines.

P.Q involves the following checks –

- 1) Data Entry
- 2) Data deletion
- 3) Data import/ export
- 4) Data printing
- 5) Data transfer on CD/ Pen drive
- 6) Data protection through password
- 7) Data integrity on storage for long time
- 8) Data compression
- 9) Access control through system pass word
- 10) Audit trail
- 11) Data protection from virus
- 12) Software integrity
- 13) Integrity of operating system

3. SELECT TRAINED PEOPLE FOR VALIDATION.

Validation is a serious exercise to be performed by specially skilled and trained individuals. Normally people commit the following errors.

Employment of unskilled /casual person for operating machine

Employing the fresh Analyst for analyzing the sample

Employing inexperienced people for recording the results

The Criteria for trained people

Well experienced and trained with the equipment under validation.

Capable of judging the chance errors during operation

Capable of reading and recording the results appropriately

Sincerer and hard working in nature

The selected and trained people shall be capable of checking the followings: following do and do not:

Check for URS

Do prepare DQ in consultation with in house validation team and proposed vendor. If possible involve skilled operators and Workmen who has to operate the machines

Do consider available space, available electrical load, environmental conditions (Immediate and External), likely noise, water and air pollution which may be caused under operating conditions.

Do consider safety aspects.

Do check operating mechanics as particular product may require specific treatment

Do check risk profile of the various components and eliminate the possible risk

Do insist for the following documents

1. Operation manual
2. Cleaning, maintenance, and calibration procedures
3. Schematic drawing and GA drawing cross sectional views
4. Calibration certificate
5. Weld certificate
6. Material certificates
7. Passivation reports
8. Wiring Diagram

Do not ignore vendor's recommendations as he knows about the machine more than you.

Do not draft DQ with out URS sight visit and discussion with Vendor.

Do not buy the machine in hurry and then perform retrospective

Check for DQ

DO not miss to specify finish of critical contact parts

Do involve vendors and consultant for DQ

Do not maintain DQ as an isolated document; always link it with purchase order.

Check for IQ:

1. Do check delivery as per Purchase Order and Design Qualification
2. Perform installation checks such as Leveling, proper bolting, and proper fitting of knocked down parts, proper connection of water and electricity.
3. Do check all material certificates, weld reports, Passivation reports & suitability.
4. Do check operation manual, SOP, SCP.
5. Do check the followings
 - a) Missing Components
 - b) Leakages c)
 - c) bad finishes d)
 - d) Design deviation e) Capacity of machine
 - e) Brand mismatch for bought out items
6. Do involve Vendor and maintenance people during installation
7. Do not approve IQ until open issues are appropriately closed
8. Do not modify the installation with out consulting vendor.

Check for OQ:

- 1) Check the operation of each component
- 2) Check the operation of machine as a whole.
- 3) Check for safety feature applied on moving parts
- 4) Check undue noise level.

- 5) Do check functioning of control panel
- 6) Do check functioning of safety lock out.
- 7) Do check proper operation of audio and visual warning signals.
- 8) Check suitability of PLC or Computer system installed along with the machine.
- 9) Do not perform OQ in absence of vendor and maintenance people.
- 10) Do prepare deviation report stating parts out of order, parts operating erratically, parts working un controlled
- 11) Do not approve OQ unless deviations are corrected.
- 12) Do check operation over a sufficient period. Just do not run and certify.
- 13) Do check operations with and without materials input.
- 14) Do check water and air pollution caused by the machine under continuous operation.
- 15) Do calibrate the gauges during OQ.
- 16) Do check clean ability of machine.

Check for PQ

- 1) Do check that DQ, IQ, OQ has been successfully performed and all open issues are solved.
- 2) Do check PQ protocol is approved and all Raw materials required for performance test are available.
- 3) Record all observations on line.
- 4) Do set acceptance criteria for all tests performed and evaluate the results against them.
- 5) Repeat PQ experiments at least 3 times. The length of each experiment shall be matching with commercial production.

Check for Cleaning Validation

- 1) Prefer Swab Test
- 2) Use swab material which is compatible with drug for which cleaning validation is perform.
- 3) Use soaking solution in which the drug has good solubility
- 4) Identify the equipment parts from where swab sampling is to be done. Do not forget to select difficult to clean parts.
- 5) Calculate the area with which drug under process comes in contact.
- 6) Develop HPLC or Spectrometric sensitive method for the analysis of swab samples. Validate the process Determine the recovery.
- 7) Express the residue report in parts per million per square feet.
- 8) Set acceptance criteria in parts per million per square feet.
- 9) Prepare SOP for swabbing and residual analysis.
- 10) Repeat cleaning validation online and on 3 consecutive runs of commercial batches
- 11) Determine residual level of each equipment

Check Process validation:

- 1) Run at least 3 commercial runs.
 - 2) Assure suitability of equipment, raw materials and utilities before production runs.
 - 3) Record all CPP accurately on line
 - 4) Analyze the sample and prepare COA
 - 5) Evaluate the data against acceptance criteria
 - 6) Note down deviation
 - 7) Check for consistency
 - 8) Do perform revalidation in case of major deviation in composition
Machine and materials
- 1) Do not conduct trial at random, always take 3 consecutive runs
 - 2) Never select batch size less than $\pm 15\%$ of commercial batch size
 - 3) Do not reject a trial if it rejects.
 - 4) Resolve failure with data supported by OOS and conduct validation on 3 fresh batches
 - 5) Do not perform process validation with dummy material. Always use actual raw material
 - 6) Do not reject validated batches if they pass. They can be released for distribution

Check Method validation:

- 1) Wash HPLC column in successive runs
- 2) Ensure system suitability before running the test
- 3) Do validate all the parameters including accuracy, precision, linearity, robustness, specificity, LOD & LOQ
- 4) Use internal standards where necessary
- 5) Preserve all material data i.e. HPLC graphs , Calculations
- 6) Take maximum readings to allow calculation of mean
- 7) Ensure that validation is performed by the team of at least 3 members. Two will perform the validation and record the results. The third person will independently verify the results
- 8) Use all standard reagents and solvents

Checks for Computer Validation:

- 1) Employ trained EDP technician to assist in validation
- 2) Do check hardware and software both and peripherals
- 3) Do check operating system
- 4) Do check security and protection system for data access
- 5) Do check audit trail function
- 6) Do check storage, deletion , input , output, graphic , printing , copying functions
- 7) Do check nonconformities of specific program
- 8) Check UPS for supply of electrical current of uniform voltage
- 9) Check for access through lane system.
- 10) Check for virus protection
- 11) Check for data recovery functions

12) Check for electronic signatures

General Checkpoints:

- 1) Protocols shall be drafted by experts who have thorough knowledge of risk factors associated with process , method or equipment.
- 2) Protocol shall be thoroughly explained to all concerned individual
- 3) All on line gauzes / instrument shall be calibrated prior to validation
- 4) Ensure that all utilities required for validation are in perfect working conditions.
- 5) Ensure that all inventories such as Raw materials are arranged in advance
- 6) Protocols shall be filled by hand and on line with the validation activities. All entries shall be initialed with date.
- 7) For process validation 3 consecutive batches are necessary.

4. ACQUIRE 100% KNOWELDGE OF VALIDATION

Just drafting the protocols on validation never provides 100% knowledge about it. One has to go beyond this and discover and acquire the knowledge in following areas:

- 1) Risk identification and analysis of the same.
- 2) Machine design
- 3) Physical / Chemical / Microbial Analysis.
- 4) Machine maintenance.
- 5) Automated / Computerized system.
- 6) Deviation control/Change Control/CAPA
- 7) Documentation and statistical analysis
- 8) cGMP
- 9) Vendor audit.
- 10) Basic Engineering
- 11) Management and Team Work

Normally it is not possible to acquire so much knowledge by a single person Hence validation is performed by team of specialized people.

5. CHECK FOR ESSENTIAL DOCUMENTS

- 1) Calibration Certificate
- 2) Supporting materials
- 3) Line diagram of equipment
- 4) Process flow diagram
- 5) Metal analysis report
- 6) Standard Operating Procedures
- 7) Welding Reports
- 8) Metal polishing Reports

- 9) General Arrangement Diagram of systems
- 10) Cross sectional views
- 11) Test print outs
- 12) Testing graphs / readings
- 13) Purchase order
- 14) Operation Manual
- 15) Maintenance procedure
- 16) Electrical Diagram
- 17) Design Calculations
- 18) Certificate of Analysis
- 19) Acceptance Criteria
- 20) Vendor Audit Report
- 21) Test Certificates
- 22) Cleaning Procedure
- 23) Training Manual
- 24) Log books
- 25) Deviation Reports

6. IDENTIFY AND INVOLVE SUPPORT FROM EXPERTS

Validation is an expert's game. It requires active supports from skilled and experienced people. The fresher have no role in validation. The external validation experts are welcome.

The active validation involves following personnel:

- 1) Skilled workmen to operate machines and to clean the area
- 2) Approved chemist for sampling and Analysis
- 3) Experienced supervisor for on line observations
- 4) Experienced Q.A / Q.C person for documentation
- 5) Qualified and experienced key persons from maintenance, Q.C / Q.A, production, R & D to draft and execute the protocol
- 6) Validation team to pre & post approval validation activities.
- 7) Expert Q.C and Q.A person to check calibration
- 8) A draftsman to prepare schematic drawings, GA diagrams
- 9) IT person for checking PLC settings and working

Example 1:

A company was aiming equipment validation by its own team over 6 months with no results. However, with the help of external support through Indian consultant the task was over with 90 days.

Example 2:

A company in Mumbai was rejected by USFDA for errors in validation. The external help through a consultant in Pune helped the company to revalidate as per FDA requirement

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General Information

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4	Years in Business	20
5	Privately owned/ Public Company	Private Ltd company
6	Number of employees	20
7	Number of employees in the field of registration procedure	15
8	Office located in	Address same as above
9	Knowledge in the chemical and pharmaceutical industry	Well versed with the current Regulatory requirements worldwide for Drug Registration.
10	Experience in the field of Active pharmaceutical ingredient API registration	Total 12 Years Experience in preparation of DMF, Registration & Answer to post submission queries, GMP Audits, etc.
11	References of successfully registered products with the drug controller	Aceclofenac, Pregabalin, Olmesartan, Docetaxel, Topotecan, Sulbactam, etc.
12	Experience in other useful fields	US-DMFs, EDMFs, CTDs, Dossiers, etc.

Contact Details

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