RESEARCH ARTICLE

# Validation as applied for Pharmaceutical Processes

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## ABSTRACT

As a part of cGMP validation is the quality assurance tool through which the drug process design assures that the process can withstand the variations during the process. Using the worst-case conditions, the critical process steps could be evaluated in the light of critical acceptance criteria. It starts with the qualification of the facility, utilities and equipment regarding the design, installation, operation and performance. Stages of PV involve the process design, process qualification, and continuous process verification. Validation may be prospective, concurrent or retrospective. Process control guidance and revalidation assures that the quality was built into the product. There should be a validation master plan; all activities are documented including protocols, reports and other supportive documents and team. For product development; traditional, continuous process verification, hybrid and design space techniques should be carried out. Cleaning validation for equipment and facility should be done on specific limits as traces of contamination may be drastic. The analytical methods if not validated will provide false results with it's consequences. Every step in the tablet manufacturing for example should be validated otherwise a deactivate procedure will have an extended impacts. Validation of sterile product manufacturing is absolutely vital. Terminal sterilization requires studies for heat distribution, penetration and biological elements used. Sterile filtration requires qualification of the facility, utilities and equipment. Invalidated sterile product manufacturing process may be life threating and risky. The end user, the regulatory bodies and the manufacturers are all wining the benefits of validation which should be the heart of the quality management systems.

**Keywords:** sterile/non sterile process validation, quality assurance tool, pharmaceutical qualification, impacts of validation.

## INTRODUCTION

Validate means check or prove the validity or accuracy, demonstrate or support of the truth of value, make or declare legally valid. The origin of the word is the mid 17th cent., from the Latin validus.[14] Validation is a documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.[7] Validation is the documented act of demonstrating that any procedure, process and activity will consistently lead to the expected results, includes qualification of systems and equipment. Process validation can be defined as, establishing documented evidence with a high degree of assurance, that specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.[8]

### Process validation and quality

The basic principle of quality assurance is that a drug should be produced that is fit for intended use, this incorporates that; quality, safety and efficacy are designed or built into the product. Quality cannot be assured merely by in-process or finished product testing. Each step of manufacturing process is controlled to assure that the finished product meet all the quality attributes including specifications. So, process validation is the collection and evaluation of data, from the process design stage through commercial production, which establishes evidence that a process is capable of consistently delivering quality product[7]. USA enforced PV for drugs under sect 501(a)(2)(B)of the Act (21US.C 351(9)(2)(B); *A drug shall deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with cGMP to assure that such drug meets the requirement of this Act as safety and has the identity and strength and meets the quality and purity characteristics, which it purports or represented to posses.*

### Process validation as QA Tool

Effective PV contributes significantly to assuring drug quality [7]. Quality assurance is the activity of providing the evidence to establish confidence that the quality function is under contron[1]. PV is a part of series of QA activities from determination of the grade of the raw materials, how well they are formulated and processed, to stability of product

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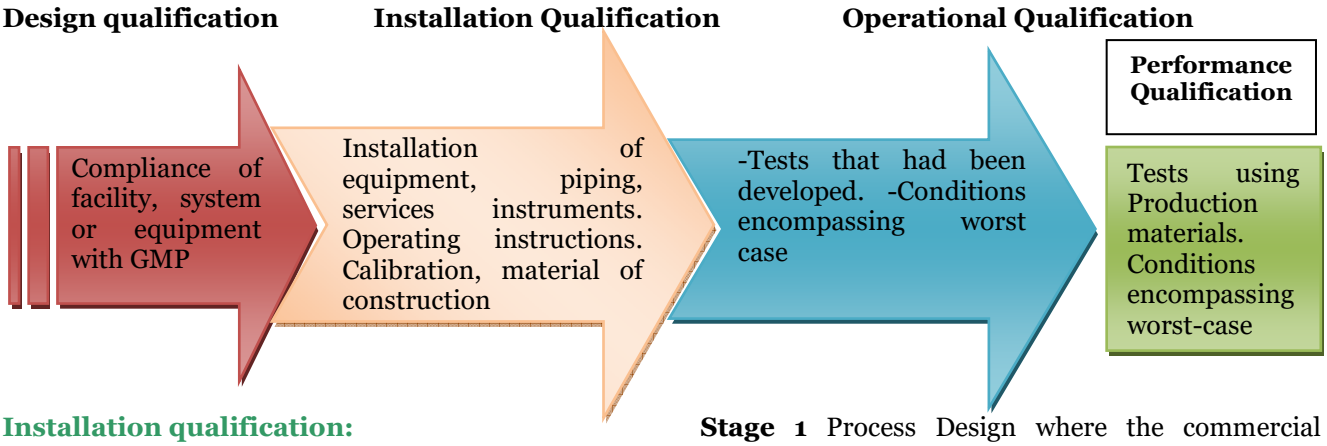
throughout its shelf-life. QA efforts in pharmaceutical development aimed to assure that a valid formulation is designed, quantify the process that will be scaled up, assist the design of the validation protocol, manufacture the bio-batches for clinical program, work with production and engineering to carry out the qualification program of the equipment, facility and systems. Develop validated analytical method for stability, testing of raw material and product release specifications. It is not surprising that PV became a vehicle through which quality assurance now carries out its commitment to cGMP[16]. During routine production Quality standards validation efforts involves equipment calibration, in-process testing and monitoring, training of personnel, development of SOPs, log book, batch production and control record are quality standards that enhance the potential for monitoring a validated process.

**Qualification**[12]

The equipment should be installed according to the requirements. Calibration, maintenance and cleaning developed as SOPs, test conducted to assure equipment operating correctly under normal and worst case and operator training are the basic principles of qualification.




**Installation qualification:**

The equipment should be checked, then the functional operating criteria being settled. Preventive maintenance, cleaning and sanitation or sterilization procedures should be documented.

**Operational qualification:**

To define the critical variables of the equipment operation, normal and worst case conditions, data from the test should conform to the pre-determined acceptance criteria. Set SOPs, services, cleaning, maintenance and calibration.

**Performance qualification:**

Modification or relocation should follow change control procedures. Data to support and verify the operating parameters and limits for the critical variables should be available. Calibration, cleaning, preventive maintenance, operational procedures and operator training should be documented.

**Process validation**

**Stages of validation activities. [7]**

**Stage 1** Process Design where the commercial manufacturing process is defined based on the knowledge gained through development and scale – up activities.

**Stage 2** Process Qualification, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

**Stage 3** Continued Process Verification, ongoing assurance is gained during routine production that the process remains in state of control.

**Types of Process validation** [18]

**Prospective validation:**

Validation carried out before routine production intended for sale. It includes; description of the process, critical processing step to be investigated, equipment/facility to be used and its calibrating status, finished product specifications, analytical methods, in–process control with acceptance criteria, additional testing, sampling plan, methods for recording and evaluating results, functions and

responsibilities of team, proposed time table, experiments on challenging condition (worst case) exercise. Then a Master Batch Documentation can be prepared, observations and sufficient data is then evaluated. Three consecutive batches are agreed parameter.

**Concurrent validation:**

Validation carried out during routine production intended for sale. It applied for processes which have a manufacturing and test history indicating consistent quality production. Previously validated strength of the product, different shape of tablets or the process is well understood.

**Retrospective validation:**

Validation of processes for a marketed product based upon accumulated manufacturing, testing and control historical batch data from batch processing, packing records, process control charts, maintenance log book, and records of personnel changes, process capability studies, finished product data and stability storage. 10 – 30 consecutive batches should be examined.

**Revalidation and Change Control**

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facility, system, equipment or process. The intent is to determine the need for action that would ensure that the revised process will result in a product of the desired quality, consistent with the approved specifications. Amendments to process and change in equipment or material which may affect the quality or/and reproducibility of the process should be validated. Revalidation to provide an assurance that, changes introduced in the process / equipment does not adversely affect process characteristics and product quality. Some processes require regular revalidation like the sterilization process.[13]

**Validation Master Plan** [17]

VMP considers the worst case and critical steps, prospective, concurrent, and retrospective and revalidation. The plan should covers, validation policy, organizational structure of validation activities, installation, and operation qualification, testing protocols for facility, utilities and equipment, testing protocols processes of products and cleaning systems, documentation and references, validation of the testing laboratory, SOPs, change control and protocols, training of personnel, organizational charts, schedule of events, sampling plan defining the points, frequency and number of samples, acceptance criteria and response to failure.

**Validation Documentation**

**Protocol:** Title, date, unique identification number, author, approval, objectives, scope, equipment /material used, calibration, procedures, SOPs, report format, acceptance criteria, responsibilities.

**Reports:** Title, date, unique reference, copy of protocol, outline and copies of procedures, results, results against acceptance criteria, signature.

**Supporting Documents:** Equipment diagram, load patterns, work flow, recorder charts, calibration report, raw data, SOPs, test report.

**Product development process validation**

Process validation is documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce medicinal product meeting its predetermined specifications and quality attributes.[6]

**Traditional process validation**

A set of points and operation parameters range are defined to ensure reproducibility. It takes place after scale –up and prior to marketing of the finished product. Data required for three consecutive production scale batches. The scheme requires information on process description, the critical processing steps monitored, product release specifications, details of analytical methods, in-process control with acceptance criteria, validation of additional testing intended to be carried out with acceptance criteria and sampling plan, methods for recording and evaluation of results, proposed time table, report on batch analytical data, certificate of analysis, batch production records, report on unusual findings and conclusion should be available.

**Continuous process verification**

Process performance is continuously monitored and evaluated. It is a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predetermined specified parameters consistently produces materials which meet all the critical quality attributes and quality strategy requirements. The scheme includes on/in /at-line monitoring including number, size and frequency of samples, analytical methods, acceptance criteria, statistical models used and contribution of monitoring to design space verification. [5]

**Hybrid approach:**

Traditional and continuous validations are applied for different steps of process.

**Design space** [9]

The multidimensional combination and interactions of input variables and process parameters that have been demonstrate to provide assurance of quality working within the design space is not considered to be a change. Commercial process is generally conducted and validated in a specific area of the design space defined as normal operation range, change of this normal operation range represent a risk and so requires verification of the suitability of the design space to ensure that the quality attributes are still being met.

**Cleaning validation**

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products. Validation is aiming to product residue, cleaning agent residue air-borne particulate and microbial contamination.

Validated analytical method having the sensitivity to detect the residue should be used. Swabs from the contact and non-contact surfaces and the final rinse sampling should be tested.

Cleaning protocols are required for at least three consecutive applications of successful procedure. Revalidation is required in case of changes to equipment, products or process and periodical. Operators should be trained in the application of validated cleaning process and are supervised.

**Equipment:**

Critical areas of the equipment should be defined, dedicated equipment is required for materials those are difficult to remove or those of high toxicity and high safety risk. Microbial growth by residual water control, period and conditions between cleaning and re-use should be specified. Detergents could be used but removal of detergent residue should be evaluated and its acceptable limits defined.

**Limits:**

Not more than 0.1% of the normal the therapeutic dose of any product will appear in maximum daily dose of the following product. Not more than 10 ppm of product will appear in another product. No quantity of residue should be visible in the equipment.[15]

Allergic ingredient, penicillin, cephaelosporins, potent steroids, cytotoxic should be below the limit of detection by best analytical equipment. This necessitates dedicated areas for such products.

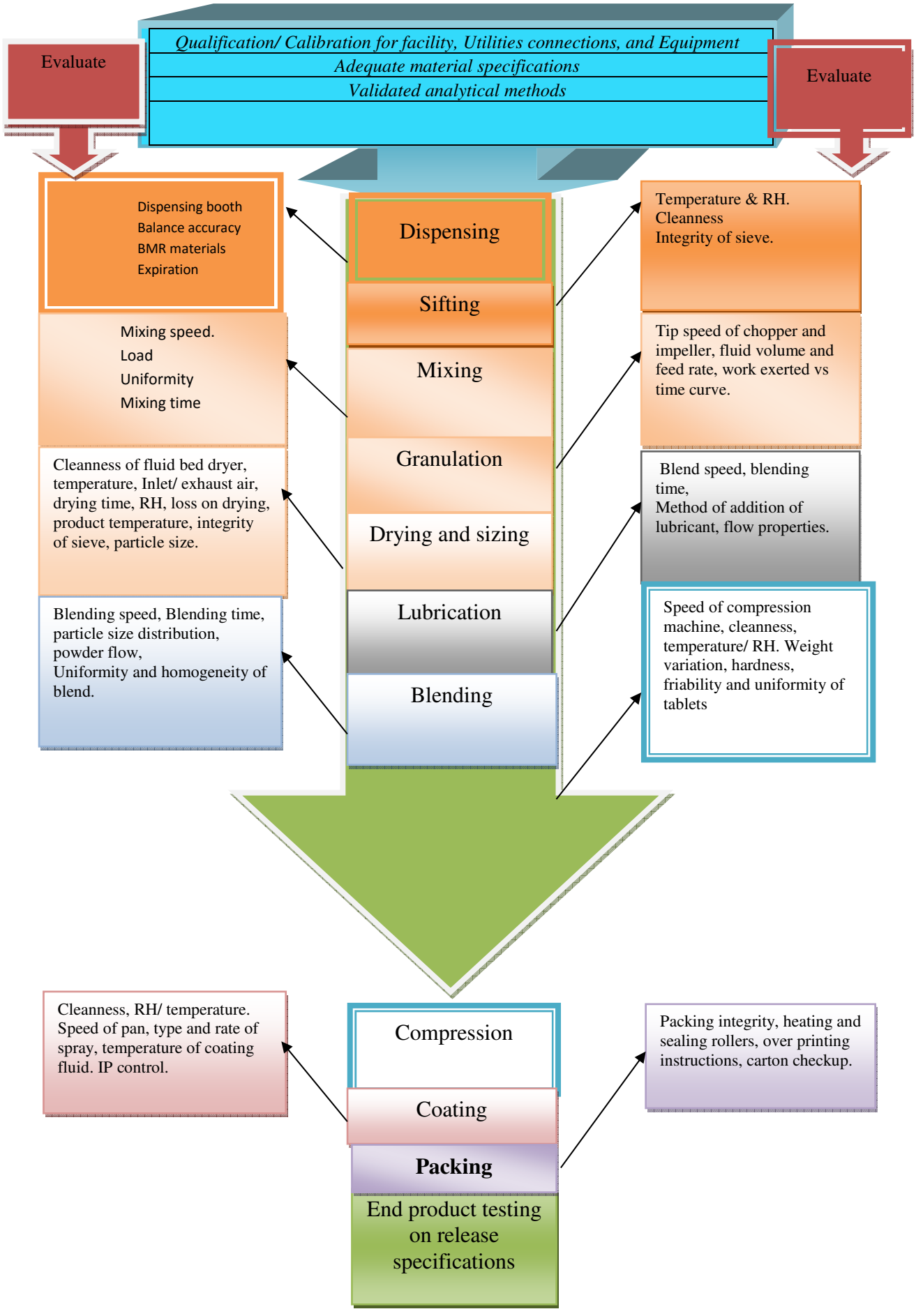
**Documentation:**

Protocol and SOPs should contain:[15] Objectives of validation process, responsibilities for performing and approving the study, description of equipment to be used, interval between end of product and cleaning process, cleaning procedure for each product and each equipment, number of cleaning cycles, routine monitoring required, sampling procedure and location, analytical methods and limit of detection, acceptance criteria, bracketing, revalidation. Report should be prepared and approved; the conclusion should state cleaning process has been validation successfully.

**Validation of analytical methods:**

Validation required for Specificity, Accuracy, Precision (repeatability and reproducibility), Limit of detection, Limit of quantification, Linearity, Range and Robustness [6]. Pharmacopeia method used for pharmacopeia material was supposed to be validated [11].

**Non-Sterile Products Validation: e.g Tablet Processing Critical Steps**



**Impacts of Invalidated Tablet Manufacturing Process**

| Component | Attributes | Quality & Productivity Risks |
|---|---|---|
| Water supply | P$^{H}$, contamination, stagnation, filters, conductivity, insufficient | Conductivity changes, Contamination, productivity |
| Weighing | Laminar flow, cross checking, RH | Cross-contamination, mix up, inaccurate quantities, |
| Mixing blending | Type, speed , time | Uniformity of content, |
| Granulation | Speed, volume of fluid, rate of addition, Cross checking | Inadequate granules, moisture, missed ingredients, |
| Drying | Temperature, time, cleaning | Cross contamination, moisture |
| Milling | Wrong mesh | particle size distribution |
| Compressed air | Moisture, oil, hydrocarbon | Contaminated product |
| Compression | Cleaning, black spots, fitness, applied pressure. Feeder | Cross contamination, hardness, friability problems |
| Environment | Temperature, RH, differential pressure, dust, air borne contaminants ,light | Degradation of material, contamination of product |
| Coating | Spray rate, angle , homogeneity of fluid, temperature, speed of pan, pressure | Elegance loss, critical in control release or enteric coating |
| Dedusting | Vacuum pump, brush | Dust, orange peel appearance |
| Packaging | Mix up, wrong information, loose | Wrong product, miss use, loss of elegance and confidence. |
| Assay | Equipment, GLP, CRS | False results |
| Dissolution | Equipment, medium and temperature | False results |
| Disintegration | Equipment, timer, GLP, medium | False results |
| Appearance tests | Consistency, color, intactness, touch conditions, personnel | Loss of elegance organism. e.g E.coli |
| Printed data | Mfd, exp, lot | misleading data |
| Stability testing | Temperature, RH, sampling, ongoing testing | False results, post marketing control. |
| Storage | conditions, temp map, mix up, dust, areas and locations ,FEFO | Degradation, deterioration of material. Expiration |
| Documentation | Unique identifying code, perfection, responsibilities, following SOPS | Confusion, no tracing Uncertainty. |
| Cleaning | Residues, retained water, SOPs, air | Contamination and cross contamination. |
| Personnel | Training on GMP & operation, gowning, behavior | disqualified procedures |

**Impacts on safety and efficacy:** Out of specifications product of uncertain quality, inconsistency and loss of elegance and appearance, sub-dose may lead to patient continue suffering from illness and its consequences and over dose may lead to toxicity and life threatening, bioavailability problems, contamination leads to infection, testing failure results in loss of materials, efforts and time, then recalls and regulatory incompliance. Company loss of reputability and resources and may lead to shutdown.

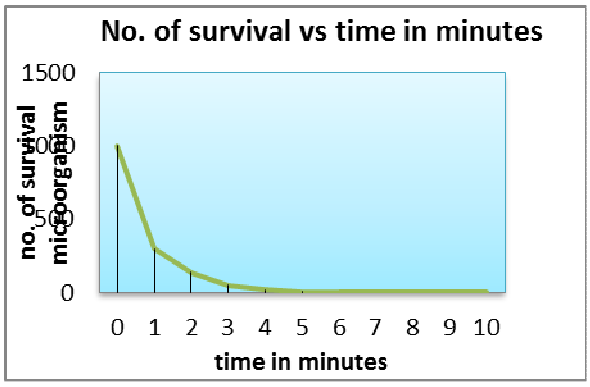
**Sterile Production validation** [2]

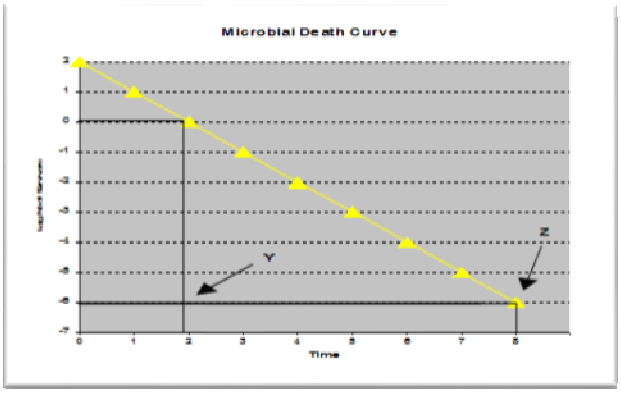
Sterile product should be free from microorganism, pyrogen and particulate, of high purity and quality. Sterilization is an absolute value; statistical sampling will not provide enough confidence. Validation should build sterility into product, demonstrate to a maximum level of probability that the process and method have established sterility to all units of the batch and provide assurance of results of end products sterility testing. Sterility Assurance Level SAL is the probability of one in a million containers being contaminated. Validation of sterile products requires theoretical approach, performance of experiments and analysis of results.

**Methods of sterilization**: Moist heat, dry heat, ethylene oxide, gamma radiation, filtration, UV, formaldehyde and hydrogen peroxide.

**A-Terminal sterilization**: moist heat, ETO, radiation.

Organisms are killed exponentially [17] that follow first order equation. D-value is the time or dose required to reduce the microbial population by one log reduction or for 90% reduction under a given set of conditions.




D= 1/b. Z–value is the temperature required for a one log reduction in the D- value. $Z=(T_2-T_1)/\log D_1-\log D_2$. F-value is the unit of lethality used to compare the relative sterilizing capacities of heat process. F-value is a measure of total process lethality. It indicates the equivalent amount of time delivered by heat process at particular temperature. $F_o=D_{121}(\text{LogA} - \text{Log B})$

**Validation Protocol** [13]

Calibration: Temperature recorder and sensors, thermocouples, pressure sensors, timers, conductivity monitor for cold water, flow meters, water level indicators and thermometers. Physical and chemical indicators should be tested for time and temperature responses. Biological indicators should be tested for count responding to time and temperature and stored appropriately within expiry. Accuracy of thermocouples should be ±0.5ºC. Error of 0.1 will result in 2.3% error in $F_o$. Qualification: Installation, operational and performance qualification should be done. Heat distribution studies: To identify slowest heating points using 10-20 thermocouples located to document and ensure that heat distribution is uniform and the cold spots determined. The difference of more than ± 2.5°C between the coolest spot and the mean chamber temperature indicates the equipment malfunction.

Heat penetration studies

To determine lowest and highest temperature locations and slowest and fastest to heat locations inside product containers, it is the most critical component in sterilization process. Container with maximum fill volume and slowest to heat solution should be used. The success of a validated cycle depends on the determination of $F_o$ value of the coolest spot inside the container located at the cool spot. The minimum $F_o$ value = 12 min.

Biological challenge studies

Spores of *Geobacillus stearothermophilus* are most commonly used (considered "worst case"). Indicators should be placed adjacent to thermocouples, at cold spots and slowest to heat locations; The USP specifies lethality input of 12D for a typical over kill approach.[17]

**B-Sterile Filtration**

Removing bacteria rather than killing it. Filtration also removes particulate matter. It avoids pyrogencity. 0.2 – 0.22 um pore size filter media are considered to be capable of producing sterile filtrate. Filter should undergo qualification tests.

**Validation of Aseptic Processing** [13]

Simulating production process conditions and using a bacterial culture medium, successful operation is to fill 4750 unit three consecutive times with zero contamination. After media fill failure, environmental monitoring data and trends, personnel monitoring data and trend, sterilization charts, HEPA filters certifications, filter integrity test data, handling and storage of all equipment should be evaluated. Validation of the solution preparation to the final container/ closing/ sealing step will provide the highest assurance that all steps in the process are controlled. Adequate simulation involves the worst–case of equipment, environment and personnel.

### Qualification of facility design and construction

**The facility:** Use HEPA filter for the air supply. Maintain positive pressure, easily cleanable surfaces. Provide temperature and humidity controls appropriate to the product, electronic particle counters, sampling of surfaces of equipment and persons.

**Utilities:** Water, clean steam and compressed air, HVAC components that affect product sterility, HEPA filter leakage, (use aerosol of air compressed in polyalphaolefins).Air borne particle control, air flow direction, air pressure differentials, temperature and humidity control. Typical compressed air contains less than 0.1 cfu/cubic feet.

### Equipment qualification:

Validation of the washer can be done practically by subjecting contaminated container cleaning process, and then tested for the residual contamination. Pyrogen is determined by validated LAL. Closure, filling and sealing/capping, should undergo validation.

**C - Invalidated Sterilization Processes Risks e.g LVP**

| Component | Defects | Quality & Productivity Risks |
|---|---|---|
| Water pretreatment | filters saturated. Pumps | equipment insufficiency, ↓ productivity, contamination |
| Water treatment | softener saturated, RO | Hard water, contamination, ↑conductivity↓, productivity |
| Distillation | Pressure gauge, temperature probe, column damage, | ↓ productivity, unrecognized water quality, malfunction of equipment |
| Piping | Rust, cracks and chips leakage, | Contamination |
| Nitrogen | Leakage Contamination | Insufficient blowing or air evacuation of containers |
| Steam generation | Water quality, Energy. safety pressure release valves, pumps | Inadequate pressure, failure of sterilization cycle. |
| Compressed air | Oil separation, dryer, filter defects | Contamination, inadequate machine run |
| Cold water | Chillers, thermostat, leakage | Delay, burden equipment |
| Environment | HEPA filters, gauges, temperature/RH, dust and debris | Contamination/ deterioration. |
| Sterilization cycle | Heat distribution & penetration | False results and failure of process. |
| Autoclave | Timer , Thermocouples, steam pressure, temperature probe | Sterilization failure, over heating defect the container. |
| Particulate inspection | Ergonometric, training | Contaminated product |
| Integrity of container | Leakage, Loose fitting | Leakage of content, contamination |
| labels | Machine defects, label sticker | Loss of elegance |
| Analytical methods | Assay, isotonicity, impurities | Uncertainty of quality , hypo /hypertonic , sub/ over dose |
| Endotoxin | CRS, incubator, trained worker | Life threatening |
| Sterility | Conditions, media, incubators, trained personnel | Contaminated released/ sterile rejected. |
| Stability | Conditions, testing plan | False results, uncertain stability |
| Storage/quarantine | Temperature/RH, rodents, load | Degradation, loss of elegance |
| Documentation | SOPs Traceability. Responsibility | randomness, and mismanagement |
| Cleaning and disinfection | Contamination | Contaminated equipment |
| Personnel | Qualification. Training on cGMP | Inadequate quality, poor performance, waste of resources. |

### Impacts on safety and efficacy

Invalidated sterile manufacturing activities are life threatening, increased recall lead to depletion of resources and finally total collapse of facility.

### Quality Risk management Tools

Failure could be evaluated by Cause and effect, (Fishbone, Ishikawa Diagrams), Fault tree analysis (FTA), Hazard Analysis and Critical Control Points (HACCP).Failure mode effect analysis (FMEA).[3] Post marketing follow-up of efficacy, adverse reactions and risk management plans to evaluate quality, safety and efficacy together with benefit-risk analysis as a quality management tool.[5]

### Benefits for manufacturers to approach validation

Validation deepens the understanding of the process, decreases the risk of processing problems and assures the smooth running of the process. It decreases the risks of the defect costs by decreasing the rejection and rework. It decreases the risks of regulatory incompliance, risk to the patient and to the manufacturer. A validated process requires a less in-process control and end product testing. It decreases complaints and recalls. It provides Customer satisfaction by using safe, effective and assured quality products which in turn increases the sales. Validation avoids process failure and ease investigations of deviations.

### Encouraging manufacturers to approach validation

Enforced by law and regulations, quality management techniques in production and QA, implementation of risk based approaches for quality management; design, personnel, environmental conditions and process.[10] Inspection policies, ongoing data analysis, computer system for management, electronic records, CTD format, process analytical technology PAT in/on/at-line facilitating continuous process to improve efficacy and consistency. Increase automation. Validation team should be one of the licensing requirements. Warning letters could be issued for incompliance.

## CONCLUSION

Drugs should be designed robustly enough to withstand the variations in the manufacturing process. Validation is the tool which can assure this. Validation is an integrated process which built quality into the product. It is the quality assurance of pharmaceutical technology and a milestone of cGMP. Regulatory bodies should make more efforts to implement validation describing the frame work and detailed guidance defining the critical steps to demonstrate process predictability. Validation is a feasible and cost effective process to manufacturers as it avoids rejection, save the resources and maintains patient confidence. Validation assures quality according to the predetermined acceptance criteria considering the worst case studies thus efficacy and safety of drugs could be guaranteed.

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