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VERIFICATION STRATEGIES FOR ESTABLISHING RELIABILITY AND VALIDITY IN PHARMACEUTICAL MANUFACTURING PROCESS- AN ENROUTE TO REGULATORY COMPLIANCE

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ABSTRACT: The Process validation involves a series of activities over the lifecycle of the product and process. The FDA guidance described three stages of process validation which includes Process Design, Process Qualification, and Continued Process Verification (CPV). The CPV stage is a never ending approach that continues throughout the entire commercial lifecycle of the product. CPV is dependent on compliance with GMP principles and ensures that manufacturing process remains in a state of control. Establishment of Critical process parameters (CPP) and assessment of Critical quality attributes (CQA) of a product ensures robust manufacturing process and thereby improves productivity and desired quality. The product stability program, change control process & annual product review process serves as key drivers for monitoring process stability. Process analytical technology (PAT) applications such as near infra red spectroscopy, raman spectroscopy & multivariate statistical process control can be viewed as enablers for CPV. The primary goal of PAT is to reduce process variabilities that may impact CQA's of a product. Continued Process verification is an effective quality risk management tool for detecting trends and implementing preventive measures prior to CQA failures. Conducting a gap analysis helps to detect discrepancies related to manufacturing process, quality control systems of a pharmaceutical industry and becomes mandatory to achieve regulatory compliance. Ensuring data integrity is an essential component of industry's responsibility to ensure safety, efficacy and quality of drugs and is a direct measure to protect the public health.

INTRODUCTION: Process Validation: USFDA (United States Food & Drug Administration) defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics".[1]

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Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing other undesirable properties.[2, 3, 4] Validation establishes that the process equipment has the capability of operating within required parameters. [5]

Validated method reduces variability between batches, ensures robustness & decreases the risk of regulatory non-compliance. Process validation serves to be the most recognised parameters of cGMP & are beneficial for Industrial manufacturing.[6] According to USFDA's current Good Manufacturing Practices (cGMP), control procedures shall be established to monitor process

output and to validate the performance of manufacturing processes so that drug products could be produced with a high degree of assurance meeting all quality attributes.[7, 8, 9, 10] EU guide to GMP (Annex 15) also refers to process validation as "The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermining specifications and quality attributes".[11]

Traditionally the development of manufacturing process involves various steps as mentioned in flow **diagram 1**.

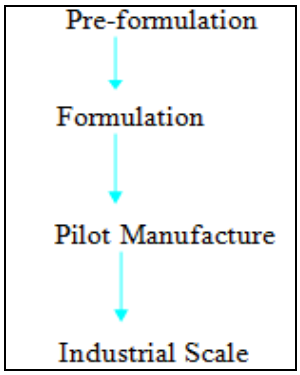

FIG.1: DEVELOPMENT OF MANUFACTURING PROCESS

A lifecycle approach for process validation is now an expectation from regulatory agencies.[12, 13] Industry experts are developing methods to implement a lifecycle approach in various stages of process validation.[14, 15, 16] A science and risk-based approach applied throughout the process lifecycle is a more holistic and robust approach as represented in flow **diagram-2**.

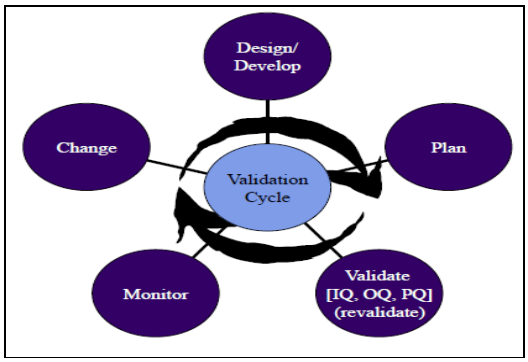

FIG.2. LIFE CYCLE APPROACH TO PROCESS VALIDATION

The basic requirements for carrying out a process validation activity are shown in **Fig.3**.

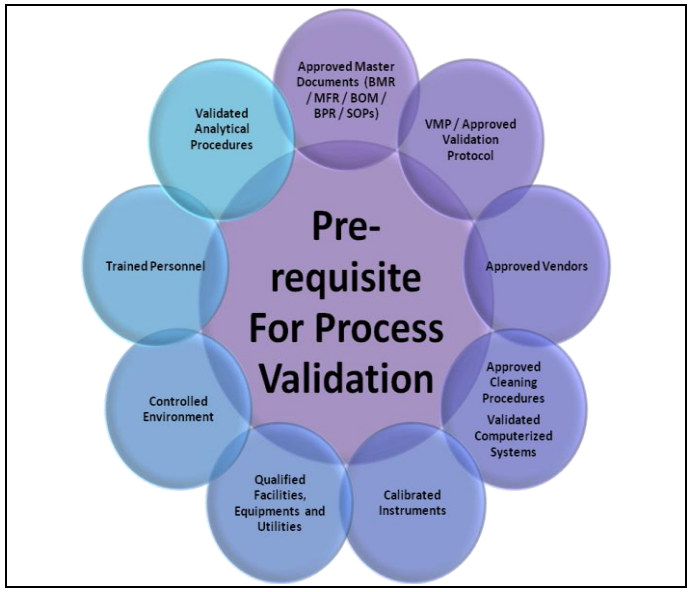

FIG.3. PRE-REQUISITE FOR PROCESS VALIDATION

Process validation ideally involves three key stages as represented in flow **diagram-4**.

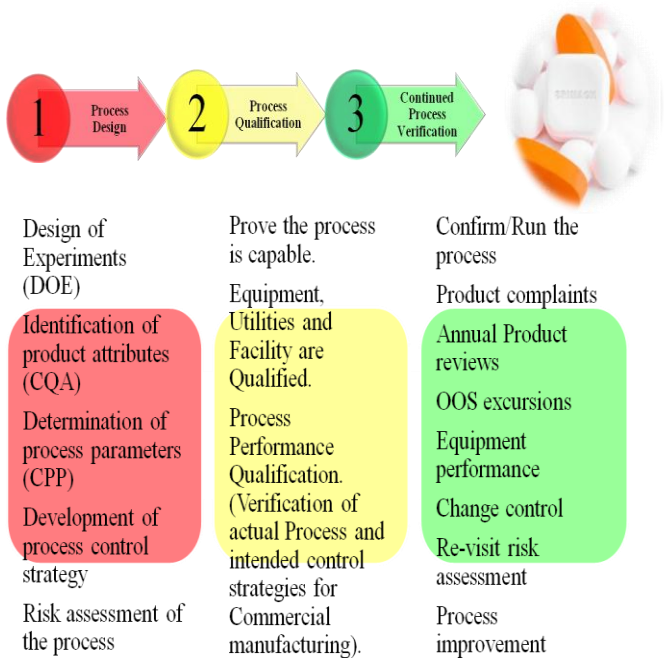

FIG.4: KEY STAGES OF PROCESS VALIDATION

The type of documentation involved in process validation includes validation master plan, validation protocol, validation reports & standard operating procedures. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning, calibration & qualification of equipments etc.[17, 18] "A Validation protocol is written plan stating how validation will be conducted, including test parameters, product

characteristics, production equipment, and decision points on what constitutes an acceptable test results". A written validation report should be available after completion of validation and must be approved/authorized by quality assurance department.[19] Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work delegation & lays down instruction to be followed for complying cGMP principles & other regulatory requirements. The other details like equipment specifications & maintenance were also included in SOPs. [20] The determination of process parameters are of paramount importance in process design stage, various regulatory guidelines uses the terminologies related to process design as mentioned below

Quality Attributes:
A physical, chemical, or microbiological property or characteristic of a material (Active Pharmaceutical Ingredient-API & excipients) that directly or indirectly impacts product quality.

Critical Quality Attributes (CQA):
A quality attribute that must be controlled within predefined limits to ensure that the product meets its intended safety, efficacy, stability and performance.

Critical Material Attributes (CMA):
A physical, chemical, biological or microbiological property or characteristic of an input material (API & excipients) that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material (finished product).

Critical Process Parameters (CPP): A process parameter that must be controlled within predefined limits to ensure the product meets its pre-defined quality attributes.

The inter relationship between CQA, CMP & CPP is mentioned **Fig.5**.

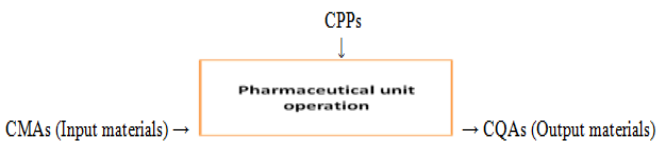

FIG. 5: RELATIONSHIP BETWEEN CQA, CMP & CPP

Based on the above relationship, linkage of patient, product & process is represented in the following **Fig.6**.

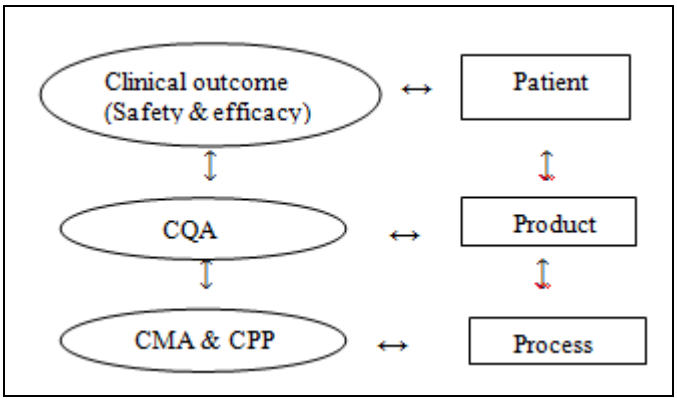

FIG. 6: LINKAGE OF PATIENT-PRODUCT-PROCESS

Applicability of Modern Manufacturing approaches in Pharmaceutical Industry:
The updated FDA regulations facilitate the implementation of novel approaches in pharmaceutical manufacturing, some of which includes:

- Six sigma coupled with lean manufacturing
- Process capability analysis
- Green chemistry
- Continuous manufacturing
- Statistical process control tools
- Advanced analytical methods (Process analytical technology)
- Real time process monitoring & control
- Proactive changes & continual improvement

Six sigma coupled with lean manufacturing:
Six sigma is a statistical concept or a quality management approach that measures a process or a product in terms of defect at six sigma level and offers a way to focus on developing and delivering perfect products and services.[21] Six sigma could help an organisation reduce defects and improve profitability using several basic tenets.[22] Six Sigma

methodologies use statistical tools to identify the vital few factors & utilises DMAIC (Define, Measure, Analyse, Implement & Control) model for improving quality of processes and generating bottom-line results.[23] The DMAIC model is depicted in figure-7. Lean means putting the right things in the right place at the right time the first time while minimizing waste and being open to change. This leads to less waste, less design time, fewer organizational layers, and fewer suppliers with more employee empowerment, more flexibility and capability, more productivity, more customer satisfaction and without a doubt, more long-term competitive success. Lean principles incorporated in the workplace today can spell business survival for the future. [24] Six Sigma lean manufacturing aims for a performance target of only 3.4 defects for every million activities. [25]

FIG.7: PHASES OF DMAIC MODEL

Process Capability Analysis:

Process capability is the comparison of ‘‘Voice of the Customer’’ (VOC) with the ‘‘Voice of the Process’’ (VOP). VOC, which is built on customer requirements, is defined by the specification limits of the process, which are fixed, while VOP is defined by control limits, which are based on performance data and vary over the time. Metrics such as capability index namely Cp and Cpk were developed several years ago to calculate this comparison between control and specification limits. [26]

The capability index is a ratio that compares process spread to tolerance spread and results in a single number. It is a management tool which is used to compare process performance. [27] A process is a combination of man, machine, materials and methods for producing a desirable & measurable output. Processes are evaluated by statistical methods and must have inherent statistical variability. The desired specification and requirement of a product or service met by the process is called process capability. Process capability index (Cpk) is the ability of the process to produce measurable output within specification constraints. The natural variation experienced by a process with respect to its specification limits are measured by process capability index. Process capability indices are formed to express highly desirable capability with an ascending higher value. The values present near or below zero highlights that process is operating at higher variation. [28]

Green chemistry in pharmaceutical manufacturing:

Green chemistry, also called sustainable chemistry, is an area of chemistry focused on the design of products and processes that minimize the use and generation of hazardous substances. [29] In pharmaceutical manufacturing, analytical procedures are involved in various stages such as the quality control of raw materials and products, effluent monitoring, pharmacokinetics, pharmacological assays, clinical trials, stability indicating assays, impurities profiling etc. The requirements related to Green Analytical Chemistry could be achieved with special attention to the use of organic solvents which are extensively involved in almost all pharmaceutical processes e.g. drug synthesis, extraction, recrystallization, dissolution of solids and chromatographic analysis. Some of the benefits of green chemistry in manufacturing include elimination or significant reduction of solvent and reagents consumption, reduction in wastes, elimination of toxic reagents’ usage & reduction of labour and energy consumption during the manufacturing process. [30]

Traditional vs Continuous manufacturing of pharmaceutical products:

The traditional manufacturing involves slow batch processing, offline laboratory testing, low equipment efficiency, avoidance of process monitoring & changes etc. In the current scenario continuous manufacturing is more preferred over traditional manufacturing techniques. In a continuous manufacturing process, input raw materials or mixtures are fed into a process train

sequentially while the processed output materials are removed continuously. The process may be run over a period of time to generate quantities of finished product with desired product quality. Suitable risk analysis, practical tests, and modelling techniques should be considered in order to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process over the full length of the required production run.

A change from batch to continuous is likely to result in changes to equipment, process parameters, control strategy, and facility or manufacturing area. A comparison of the two processes and the input materials (or formulation) is a starting point for assessing the risk of the process change. Continuous manufacturing may also have more complex in-process controls and monitoring with the potential for unintended failure modes, which have to be considered in setting a robust control system.

Handling of non-conformities for continuous manufacturing and batch manufacturing are generally similar. Continuous processing may pose challenges due to performance of the equipment, which occur gradually over a long period and hence which are not easily observed during batch processing or short tests runs. Sudden equipment failures can occur which have to be addressed. The control system has to be designed in a way that those effects are detected and addressed. Continuous manufacturing provides opportunities for improvement in pharmaceutical manufacturing including:

- An integrated process with fewer steps (e.g. safer, faster response times, more efficient & shorter times)
- An enhanced development approach (Quality by Design-QbD, Process Analytical Technology) and
- Real time product quality information

Hot Melt Extrusion (HME) is one such continuous manufacturing process that combines multiple batch unit operations in one single process. Different process steps, such as mixing, melting, homogenization, and shaping, can be performed, offering the opportunities for automation of the manufacturing plant to limit material loss, increase the throughput, decrease energy input, and yield a product with high quality. During the continuous manufacturing process, any breakdown in the processing equipment should also be investigated. A procedure can often be established for the use of alternative testing or monitoring approaches in cases of equipment failure.

The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality. For continuous manufacturing processes, it is important to consider raw material variability as a potential root cause when performing an investigation.

In a batch process, multiple raw material batches are typically mixed at the start of manufacturing. This may not be true for continuous manufacturing, where different lots of raw material can be used during the production campaign. Multiple raw material lots used in a single product batch, though they might meet specification, could introduce variability into the finished product. A change from batch to continuous manufacturing typically necessitates establishing physicochemical equivalency. Evaluation of a change from batch to continuous operation could include a comparison of individual unit operations, process parameters, equipment, CQAs, and the control strategy. Comparative batch data, particularly with respect to physical properties, impurity profiles, and drug release profiles, and bridging stability data can be helpful to support chemical equivalency.

The FDA Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance specifically identifies that the introduction of continuous processing may be one of the outcomes from the adoption of a scientific risk-based approach to process design.[31]

Statistical process control tools:

The process validation guidance recommends the use of statistical process control techniques for measuring and evaluating process stability and

process capability. The two main goals of data analysis for process validations are:

- To demonstrate the understanding of the process variation and
- To demonstrate that the process control plan works (i.e., that the process consistently conforms to requirements).

This can be achieved by performing a capability study that measures the ability of the process to consistently meet the specifications. Descriptive statistics or summary statistics are used to summarize a collection of data. Descriptive statistics is used to demonstrate that the manufacturer measures critical to quality attributes and understands degree of variation. Descriptive statistics includes average, range, standard deviation, and relative standard deviation (RSD), which are widely used to analyze data for process validation. One example of descriptive statistics is to present the data(s) in the form of normal distribution curve. The descriptive statistics is a minimum requirement that should be included in any process validation report for data analysis.

The most common applications of descriptive statistics in pharma industry includes evaluation of blend uniformity, content uniformity and tablet compression physical parameters such as weight, hardness, and thickness etc.

Statistical process control charts are required to identify process variations some of which includes variations within equipment, humidity, formulation temperature, variations due to unusual events such as tool wear, accumulation of powder on tablet press during compression process & broken parts of equipment etc. Process control charts are classified into attribute charts for counting the datas & variable control charts for measuring the datas. Some examples of control charts include Xbar & S-charts (mean & standard deviation), Xbar & R-charts (mean & range). Statistical software such as minitab is commonly used to construct control charts [32].

Advanced analytical methods (Process Analytical Technology): The primary goal of PAT is to provide processes which consistently generate products of predetermined quality. PAT implementation involves the design of manufacturing processes based on a thorough scientific understanding of the solid-state properties and stability of the components of the drug product at critical points throughout manufacturing stage. PAT enables us to understand and control the manufacturing process through the application of integrated chemical, physical, microbiological, mathematical and risk analysis methods.

The PAT concept is embraced in the quality-by-design (QbD) framework, which endorses a control strategy that considers not only risk assessment, prior knowledge, and enhanced process understanding, but also how unit operations affect the quality and stability of the product. Near Infra Red Spectroscopy (NIRS) in diffuse reflectance mode & Raman Spectroscopy are the two promising tools for process monitoring, providing valuable information to assist in product development and ultimately to ensure better in-process quality control. Analysis of blend uniformity is a critical component of batch release during the manufacturing stage from granulation (blending stage) to the compression of tablets & blending stage to the capsule filling step in hard gelatin capsule formulation.

Traditionally, blend analysis involves the use of a sample thief (sampling rod) to collect powder samples from the powder bed for analysis of active ingredient content and determination of blend homogeneity. However, this conventional method of blend monitoring suffers from serious drawbacks such as inconsistent sampling from blender (octagonal/double cone etc), non-homogeneity & failure of blend uniformity testing results etc.

NIRS has been used for blend homogeneity assessment from thieved powder samples [33], by online monitoring from a single point [34] and through multiple optical ports mounted on the blender.[35] The statistical tools such as Principal Component Regression (PCR), Partial Least Squares (PLS) & Multi-term Linear Regression (MLR) are widely used for developing a quantitative NIR calibration model for evaluating blend uniformity results.[36]

NIRS provides a means for a rapid, noninvasive at-line, on-line, or in-line monitoring and real-time optimal control of a tablet film coating processes. The ability of NIRS to predict the drug dissolution of sustained release film coated tablets and the effect of film coat thickness and film coat uniformity on both drug dissolution rate and NIR spectra have been studied by several workers.[37, 38, 39]

Application of NIR spectroscopy for orbifloxacin tablets coating process using various blends of Eudragit RL/RS was investigated. In order to make real time measurements, a diffuse reflectance probe was positioned inside the pan during coating operation. Individual and combined calibrations were developed to measure coat thickness for sustained release tablets coated with various blends of Eudragit copolymers utilising statistical tools like PLS & PCR. The ability of NIR spectroscopy to predict dissolution profile and percentage drug release from various blends of Eudragit copolymers was examined for film coated tablets of orbifloxacin.[40]

Real time process monitoring & control:

Real Time Release Testing (RTRT) in production is "the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls. RTRT is an element of the control strategy in which tests and/or monitoring can be performed as in process testing rather than tested on the end product. RTRT can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in process or end product specification. Material attributes can be assessed using direct and/or indirect process analytical methods.

The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes. Quality Target Product Profile (QTPP) refers to prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Regulatory agencies demands for detailed information about input material controls and process controls that should still be provided in the appropriate Common Technical Documents (CTD) format sections (e.g., drug substance, control of excipients, description of manufacturing process and process controls, control of critical steps and intermediates etc) for dossier submissions. A control strategy is designed to ensure that a product of required quality will be produced consistently.

The elements of control strategy mentioned in product dossier for registration should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the critical process parameters and material attributes. A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing & some other elements are as mentioned below

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality.
- Product specification(s).
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution).
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability.

Sources of variability that can have an impact on product quality should be identified, appropriately understood, and subsequently controlled.[41]

Proactive changes & continual improvement:

With the advancement of QA principles and concepts, Quality Management Systems (QMSs) have evolved to be more proactive to include change control, supplier and internal auditing, risk management, lagging and leading metric collection and review. Early implementation of quality by design concepts and practices within the frame work of QMS and ensures quality in all processes and provide the foundation for good investigation and continuous improvement. Both quality and manufacturing department therefore share the common goal of supplying high quality product through the efficient execution of their processes.[42]

The FDA/ICH (International Conference on Harmonisation) Guidance for Industry Q10 Pharmaceutical Quality System guidance document demonstrated a complete transition from attempting to control change to managing changes for process improvement. The goals allow pharmaceutical manufacturers, not only to achieve compliance but to gain business advantage. A well defined change management system should enable manufacturers to leverage opportunities to adopt more modern technologies and implement continuous improvement initiatives. Because flexibility and change are the precursors to improvement, any change-management system should be conceived so that it provides an opportunity for continuous improvement. Leveraging change management for process improvement can be compared to driving an automobile on four wheels. Each of the wheels must be equally strong and balanced if the ride is to be smooth. For change management, the wheels are:

- Awareness
- A proactive approach
- Interdepartmental communication
- Timeliness.

Depending upon the criticality of the change, some changes may even affect the safety, identity, strength, quality, or purity (SISPQ) of the product. Others may trigger the need for new regulatory filings. Managing all this change is perhaps the most important part of any life-sciences quality program.[43]

A comprehensive corrective action and preventive action (CAPA) program has been identified as a strong indicator of a robust quality culture. Continual improvement is based on preventing the initial occurrence (preventive action) or recurrences (corrective action) of a detected nonconformity or other undesirable situation. Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. FDA suggests using quality metrics as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment could contribute for continual improvement. Some of the quality metrics for each product & establishment suggested by FDA includes the following [44]:

- Lot acceptance rate
- Product quality complaint rate
- Invalidated Out Of Specification (OOS) rate
- Annual Product Review (APR) or Product Quality Review (PQR) rate

Finally the enroute to quality and regulatory compliance is depicted in the following diagram

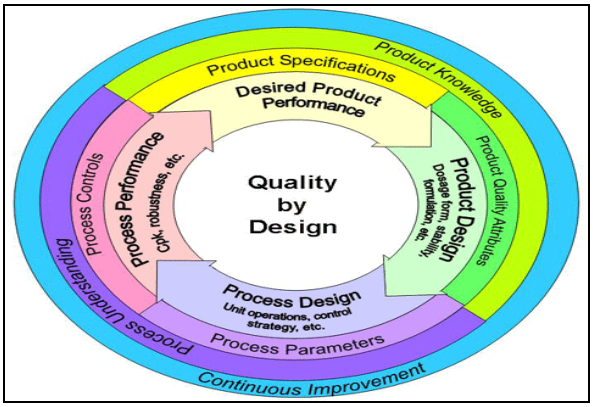

FIG 8: QUALITY AND REGULATORY COMPLIANCE CHART

Continuous Process Verification (CPV) and Continued Process Verification (CPV) of Drug products:

CPV is a science and risk-based real-time approach to verify and demonstrate that a process operates within the predefined specified parameters consistently produces material which meets all its critical quality attributes (CQAs) and control strategy requirements. CPV is a phase-3 process validation approach designed to collect and analyse product & process data that directly relates to a product quality.

The data should include relevant process statistical trends and quality of incoming materials or components, in-process material, and finished products. Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. The scope and extent of continuous process verification will be influenced by a number of factors including:

- Prior development and manufacturing knowledge from similar products and/or processes.
- The extent of process understanding gained from development studies and commercial manufacturing experience.
- The complexity of the product and/or manufacturing process;
- The level of process automation and analytical technologies used;
- For legacy products, with reference to the product lifecycle, process robustness and Manufacturing history since point of commercialization as appropriate.

CPV versus CPV of Drug Products:

Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Continued Process Verification:

It is a third stage process validation lifecycle after design and qualification. The goal is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture.

CPV would be considered the most appropriate method for validating continuous manufacturing processes. Actual data generated during continuous process verification at production scale should be available at the site for inspection. CPV is dependent on compliance with GMP principles and requirements. CPV can be introduced at any time in the lifecycle of the product. It can be used for the initial commercial production, to re-validate commercialised products as part of process changes or to support continual improvement[45]. It is recommended that the manufacturers use quantitative statistical methods wherever appropriate & feasible. Scrutiny of intra-batch & inter-batch variation is a part of comprehensive CPV program under 21 CFR Part 211.180.

The following items needs to be reviewed to during CPV.

- Product and process data
- Relevant process trends
- Quality of incoming materials or components
- In-process material
- Finished products
- Defect complaints
- OOS findings & non conformances
- Deviations & its trend
- Yield variations
- Batch records
- Incoming raw material records
- Statistical analysis of data & control charting
- Adverse event reports

- Production operator and quality staff feedback

The following **Fig. 9** and **10** shows critical parameters which needs to be controlled during the development of solid dosage forms and is an important requirement for CPV of pharmaceuticals.

FIG. 9: UNIT OPERATIONS (GRANULATION STAGE) & CONTROL PARAMETERS

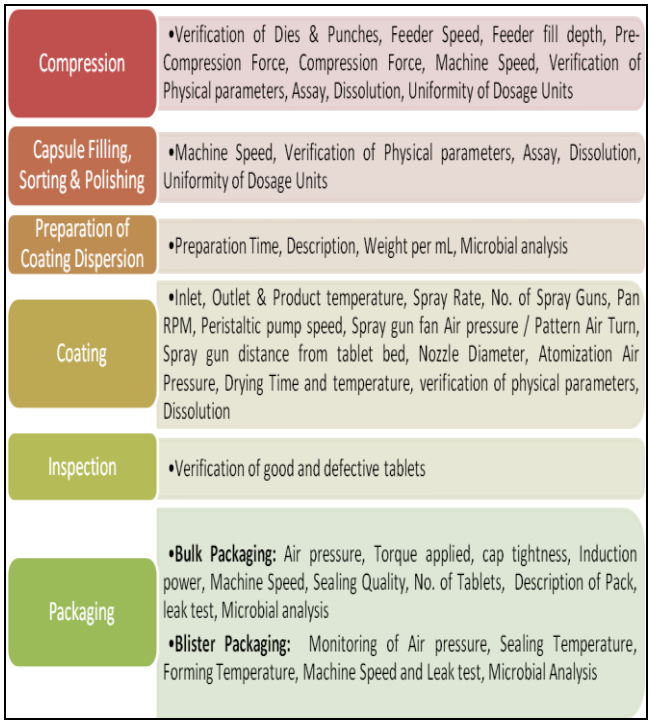

FIG. 10: UNIT OPERATIONS (COMPRESSION, COATING, INSPECTION & PACKAGING) & CONTROL PARAMETERS

In case of liquid oral manufacturing, continuous process verification is required to monitor critical parameters for suspensions that include:

- API micronisation
- Colloid milling
- Homogenisation
- Filling
- Particle size distribution,
- Viscosity
- Fill volume/weight variation
- pH & dissolution etc.

In case of liquid oral manufacturing, continuous process verification is required to monitor critical parameters for solutions/elixirs etc that include:

- Mixing time & condition to obtain clear solution
- Specific gravity
- Clarity of solutions
- pH
- Fill volume/weight variation etc**.**

In case of parenteral manufacturing, continuous process verification is required to monitor critical parameters for sterile products that include:

- Weighing (APIs/Excipients) & solution preparation
- Filtration & clarification
- Ampoule washing (water temperature, water pressure, washer velocity etc)
- Ampoule depyrogenation (conveyor belt velocity, chamber temperature etc)

- Ampoule filling (solution flow, volume to fill)
- Ampoule sealing (Flame temperature, ampoule height)
- Sterilisation (Time, temperature)
- Visual inspection (Rotation speed, brake position, Light intensity & sensitivity etc)
- Ampoule labelling (Label, ring quality & quantity, bar code, batch & expiry date printing etc)
- Packaging (blister formation, tray collocation/pressing, tray cut, leaflet, carton box, batch printing etc)

Hybrid Approach:

For some complex processes involving vast number of critical steps, traditional process validation or continuous process verification can't serve as a sole validation tool. In such situations, a hybrid i.e., combination of traditional process validation and continuous process verification can be employed and this approach is justified by the claimant. The state of control in pharmaceutical manufacturing is referred to the condition in which the set of controls consistently provides assurance of continued process performance and product quality. The information regarding the implementation of hybrid validation approach and its stage of implementation is described in the dossier.[46]

Continuous Quality Verification in Pharmaceutical manufacturing:

Continuous Quality Verification (CQV) is an alternative process validation approach whereby the desired quality attributes are ensured through continuous assessment during manufacture that is based on risk and science based approach. CQV serves as an alternative to reliance on data generated from a few production lots. CQV moves away from validation as a discrete exercise and is consistent with a lifecycle approach to process validation. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch replacing a conventional process validation approach (e.g., 3-batch validation at set-point) that was historically used. As per the definition of American Society for Testing and Materials (ASTM) standards, CQV is described as an approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary. Some of the advantages of applying CQV in pharmaceutical/biopharmaceutical manufacturing include:

- Risk mitigation
- Reduction in process variability
- Enhancement in process capability
- Enhancement in process design space
- Improvement in product quality

CQV may be applied to manufacturing processes that use monitoring systems that provide frequent and objective measurement of process data. As CQV is built in with PAT-based manufacturing and process control strategies, traditional end product testing and tight product specifications become less significant and the state of "real time release" becomes more possible. These processes may or may not employ in-, on-, or at-line analyzers/controllers that monitor, measure, analyze, and control the process performance. The associated processes may or may not have a design space.[47]

Process validation for legacy products:

A legacy product is one that is no longer under active development but has yet to be fully retired. Legacy products, which are products developed in the past but still exist on the market. The lack of new molecules and the challenges in registering new products, due to increasingly stringent requirements from preclinical and clinical through to registration phases, are driving many pharmaceutical companies to revamp old products in their portfolio. Based on the brief overview of EMA and FDA guidelines on process validation, it could be deduced that legacy products are excluded from the commonly described fields of

applications. However, through a combination of both approaches and risk analysis tools, it is possible to perform process validation of such products without referring to the traditional approach but to new techniques (e.g., fishbone analysis, risk-analysis tools such as failure mode, effects, and criticality analysis [FMECA], and logical approach) that are used by pharmaceutical companies.

ICH Q9 guidelines for quality risk management describe a wide variety of risk analysis tools for legacy products & new molecules. The goal of the risk assessment is to evaluate all the single process phases, gain more knowledge of the process itself, and also determine the appropriate control level during validation phases, so that by applying that defined process, a safe and efficacious product is always obtained. According to quality risk management principles, a Risk Priority Number (RPN) is calculated for all products during the course of manufacture & the data is collected during the initial phase of product development. The RPN for a particular product (applicable for legacy and new product) is calculated by the formula:

RPN = S x D x P x F, where S – severity, D- Detectability, P- Probability & F – Impacted phase. The RPN Threshold value is expressed as $RPN_{threshold} > X$, where X is the threshold value above which additional controls are needed during the phase of manufacturing. Using this approach the possible causes of product out of specification could be analyzed. The aim is to find weak points of the manufacturing process.[48]

Importance of Gap Analysis in Process Validation of Pharmaceuticals:

A GAP Analysis is a technique for determining the steps to be taken in moving from a current state to a desired state. It is sometimes called a "need-gap analysis", "needs analysis" or "needs assessment". Gap analyses are designed to identify deficiencies in various aspects of manufacturing & validation. In lay man term gap analysis addresses/bridges the "gap" between "where you are" & "where you want to be"& makes one to understand "what will be covered & what will not be covered". Gap analysis needs to be planned in such a manner so as to define the issue to be addressed during manufacturing process based on science & technology & risks associated with it. The developed plan is then reviewed & approved by all stakeholders (Quality Assurance, Quality Control, Regulatory Affairs, Production, Management & technical services etc). A gap analysis can often be performed by responding to a series of questions. The process involved can include the following six steps and can be accomplished using an in-depth questionnaire developed from the standards being implemented:

- Identify and evaluate the current procedures.
- Evaluate the current outcomes, preparations, & services produced.
- Identify the new standards to be implemented.
- Define the processes to achieve the new standards.
- Document the GAP that exists.
- Develop a plan to "fill the GAP" and meet the standards.[49]

The below mentioned item is an example that refers to some set of questions used in manufacturing/validation operations of a pharmaceutical facility to conduct a gap analysis.

- Does the way you currently conduct process validation program meet the predefined requirements?
- Are there technology transfer documents availabe, which are used to develop appropriate validation strategy?
- Do you perform proper statistical analysis of collected data during the process qualification as well as in continuous monitoring stages of a validation program?
- Do you have necessary statistical control charts?

- Do you have adequate environmental monitoring procedures for the pharmaceutical processing and whether it is complying with current regulatory standards?

- Do you have change control program, Corrective and Preventive Action (CAPA) systems in place? & does it contain a risk assessment component in it?

Importance of Data Integrity in pharmaceutical Industries:

Data integrity is critical to regulatory compliance and the fundamental reason for 21 Code of Federal Regulations (CFR) part 11 that sets forth the USFDA's guidelines on using electronic records (e-recs) and electronic signatures (e-sigs). Part 11, as it's commonly called, defines the criteria under which electronic records and electronic signatures are considered to be accurate, authentic, trustworthy, reliable, confidential, and equivalent to paper records and handwritten signatures on paper. In addition, this is the definition of data integrity that USFDA uses for internal training: "Data are of high quality if they are fit for their intended uses in operations, decision-making and planning . . . as data volume increases, the question of internal consistency within data becomes paramount…."that needs to be followed in regulated pharmaceutical industries.

E-Records:

Part 11 applies to records required to be maintained under the applicable regulation requirements:

- That is maintained in electronic format in place of paper format.

- That is maintained in addition to paper format and that are relied upon to perform regulated activities

E-Signatures:

Part 11 is applicable to e-sigs that are intended to be the equivalent of:

- Handwritten signatures & Handwritten Initials

- Other general signings required by the applicable regulations impacting a computer system

Some of the general features of 21 CFR Part 11 include the following:

- Closed System

- Validated Compliance

- Accurate and Complete Records

- Records in Human Readable Form

- Records Easily Retrieved

- Access Controls

- Secure, Computer-Generated, Time-Stamped Audit Trails

- Rules Enforced Workflows

- Electronic Signatures Bound to Electronic Records.[50]

21 CFR Part 11 might really be called the "Data Integrity Act". USFDA uses the acronym "ALCOA" to define its expectations of electronic data. ALCOA may be considered the data quality attributes focused on doing it right the first time when it is done, i.e., task based. ALCOA is explained as:

- Attributable – means who acquired the data or performed an action (or modification) and when.

- Long-lasting (legible) – means data is permanent and easily read (by a human).

- Contemporaneous – means data documented at the time of the activity (promptly).

- Original – means the first recording of data, raw or source data, or a certified true copy.

- Accurate – means data is correct including context/meaning (e.g., metadata) and edits.[51]

The term "metadata" describes the attributes of other data, and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual.

The acronym ALCOA+ stands for ALCOA in addition to the following attributes:

- **C**omplete – means data includes all data (passing or otherwise) from all actions taken to obtain the required information, including metadata (e.g., audit trail) and edits.

- **C**onsistent – means data is created in a repeatable and comparative manner (traceable).

- Enduring – means data stored on media proven for the record retention period.

- **A**vailable – means data readily accessible in human readable form for review throughout the retention period for the record.

ALCOA+ may be considered the data quality attributes that are focused on establishing and monitoring the support processes around data activities, continuous improvement and overall product quality. So in order to achieve overall data quality and associated product quality, one must have both ALCOA and ALCOA+. Therefore, one can infer that Product Quality is directly associated with Data Quality[52].

The UK-MHRA (United Kingdom Medicines and Healthcare Products Regulatory Agency) guideline also emphasizes the importance of data integrity. Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality. MHRA defines data integrity as "The extent to which all data are complete, consistent and accurate throughout the data lifecycle". Data lifecycle means "All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive/ retrieval and destruction". Data may be generated by (i) a paper-based record of a manual observation, or (ii) in terms of equipment, a spectrum of simple machines through to complex highly configurable computerised systems.

The inherent risks to data integrity may differ depending upon the degree to which data (or the system generating or using the data) can be configured, and therefore potentially manipulated. Data integrity requirements apply equally to manual (paper) and electronic data. There should be a procedure which describes the process for the review and approval of data, including raw data. The term raw data (true copy) means "data generated in paper format which may be retained for example by scanning, provided that there is a process in place to ensure that the copy is verified to ensure its completeness".

Data review must also include a review of relevant metadata, including audit trail. The term audit trail means "Metadata that are a record of GMP critical information (for example the change or deletion of GMP relevant data), which permit the reconstruction of GMP activities in a pharmaceutical setting".[53] As per USFDA guideline, audit trail is a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to creation, modification or deletion of an electronic record. An audit trail is a chronology of "who, what, when and why" of a record. Audit trail records are more commonly observed in chromatographic systems (HPLC, GC, LCMSMS etc) of an analytical drug testing laboratory. CGMP compliant record keeping practices prevent data from being lost or obscured in manufacturing premises.[54]

Data integrity and Computer System Validation (CSV):

Software validation is a comprehensive and methodical approach that ensures that a software program does what it's intended to do and works in an environment as intended. There is a close relation between data integrity and software

validation for computer systems and it's applications in pharmaceutical manufacturing and quality control. CSV is a systematic approach to verify that computerised systems acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly.

This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other. Computer System Validation (CSV) requires that all aspects of the validation are documented formally to ensure that there is proof that the system(s) works as intended in its actual environment.

A typical CSV lifecycle involves the following phases:

- The Master Validation and Project Plans
- User Requirement Specifications (URS)
- Design Specifications
- Risk Assessments
- Validation Protocols including Qualification documents
- Requirement Traceability Matrix or (RTM)
- Summary Report (including Deviation Management)
- Change Control &
- Periodic Review

Currently the approach taken to carry out these activities relies heavily on paper based systems such as MS Word and MS Excel where documents are manually walked around for pre and post approval.[55]

Performance Metrics and Product Quality Review:

In regulated pharmaceutical industries, finished product quality is of utmost importance as it would have direct impact on consumer health and society. Industries often use Key Performance Indicators (KPI) to assess product/process performance and sets benchmark to review product quality. An ideal GMP driven pharmaceutical industry utilises the following KPI's which would be subject to national and international regulatory audits:

- Deviations
- OOS (Out Of Specification) & OOT (Out of Trend)
- Lot/Batch acceptance rate
- Change control
- Customer complaints
- Self inspection
- External Inspection (Customer/Regulatory inspection)
- CAPA (Corrective and Preventive Action)
- Vendor Qualification (for Raw materials/excipients/packaging materials/machineries etc)
- Logistics & supply chain metrics
- Recalls/Returned products
- Reprocessing/Re-work/Re-dressing
- Ongoing Qualification
- Training Program for employees (GMP/GLP/GCP/Safety & first aid etc)
- Equipment Status – Calibration/Preventive Maintenance program
- New product launch
- Licences, COPP (Certificate of Pharmaceutical Product) etc
- Site Transfer Projects and technology transfer status.

Performance metrics (also called quality metrics) are widely used throughout the pharmaceutical industry to monitor quality control systems and processes, and many of the components that inform those metrics (e.g., data on process capability

output or statistical process control) are already collected and maintained as part of cGMP compliance. Continuous process verification of every batch of products is subjected to statistical analysis to evaluate their performance and is included in annual product quality review reports. Thus development of a broad-based quality metrics program could allow manufacturers to promote and publicize their own quality data as part of their marketing strategy which benchmarks their performance against global regulatory standards.

CONCLUSION: The approach to implement continuous/continued performance verification is of paramount importance in GMP approved pharmaceutical industries so as to ensure the reliability and validity of manufacturing of commercial batches of finished products. CPV is an integral part of process validation program and must be considered throughout the product lifecycle. A structured and customised validation program would produce high quality pharmaceutical product, as USFDA states that "End product testing alone does not promise the quality of product, but quality must be built during the process design of validation stage and quality remain stable/unaltered till product reaches the consumer". Novel approaches like six sigma-lean manufacturing is more successful in non-pharma field, yet new case studies need to be performed to adopt such practices in pharmaceutical industries as it benefits the manufacturer by reducing process variations & time consumption.

Data integrity and authenticity in all stages of processing, testing and packing of pharma products must be ensured and becomes sole responsibility of the industrialists. Globally in recent years, USFDA has increasingly observed data integrity-related CGMP violations that have led to numerous enforcements including 483's, warning letters, import alerts & consent decrees. Various regulatory agencies including USFDA expects that Quality culture needs to be built, encouraged and followed in every pharmaceutical industries to prevent non-compliance and thereby promoting integrated standards to produce safer and quality products.

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REFERENCES:

1. Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz. Pharmaceutical Dosage Forms-Tablets. 2nd ed. Vol 3. Marcel Dekker. Inc, New York, 1990, 417-447.
2. Paruchuri R, Trivedi S, Pavuluri G, Prasanthi B, Kumar S. Process Validation of Finasteride Tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(1): 11-28
3. Nash RA, Wachter HA. Pharmaceutical Process Validation. 3rd ed. Marcel Dekker. Inc, New York, 2003, 159-180.
4. Armbruster D, Feldsien T. Applying HACCP to Pharmaceutical Process Validation Pharmaceutical Technology, 2000; 24(10):170 -178.
5. Thaduvai R, Rao BS, Jeybaskaran M. Process Validation of Pantoprazole 40mg Tablets. The Pharma Innovation, 2012; 1: 47-62.
6. Parida R. Overview of Pharmaceutical Validation and Process Controls in Drug Development. Pelagia Research Library, 2010; 1(1): 11-19.
7. Chows S. Pharmaceutical validation and process control in drug development. Drug Information Journal, 1997; 31: 1195-1201.
8. Good Manufacturing Practices for Pharmaceutical Products. WHO Expert Committee on Specifications for Pharmaceutical Preparations (1992).32nd Report, WHO Technical Report Series no.823. Geneva: WHO, 14-96
9. Kumar S, Chakraborthy GS, Kumar P, Yadav AS, Seth AK et al. Process validation of Azifastm500 mg tablet. Journal of Advances in Pharmacy and Healthcare Research, 2011; 1(2): 3-9.
10. A WHO guide to GMP (1997); Requirements, part 2: Validation.
11. http://ec.europa.eu/health/files/gmp/201402_pc_draft_gmp_annex.pdf. Date of retrieval: 16 April 2016.
12. FDA, Guidance for Industry—Process Validation: General Principles and Practices (Rockville, MD, January 2011).
13. EMA, Draft Guideline on Process Validation (Mar. 29, 2012).
14. PDA, Technical Report 60, Process Validation: A Lifecycle Approach (Feb.2013).
15. Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing, Edited by Mollah et al., (John Wiley & Sons, 2013).
16. Hamid Mollah A and Bozzone S. "Process Lifecycle Validation," in Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing, Mollah et al. Eds, pages 179-225 (John Wiley & Sons, 2013).
17. South African Guide to Good Manufacturing Practice, Medicines Control Council, 1996.
18. Evans P K. Streamlining Validation. Pharmaceutical Technology Europe, 1998; 10(12): 48-52.
19. Good Manufacturing Practices for Pharmaceutical products, WHO Expert Committee on specifications for pharmaceutical preparations, 32nd Report, WHO Technical Report Series no. 823, WHO, Geneva, 1992; 14-96

20. Lambert J. Validation Guidelines for Pharmaceutical Dosage Forms. Health Canada/Health Products and Food Branch Inspectorate, 2004; 7- 15.
21. Palkar M, Rajadhyaksha P, Shah M, Shedge A, Goyal G. Application of six sigma in pharmaceutical industries. Presented at 59th Indian Pharmacy congress; 2007 Dec; Varanasi, India.
22. Goeke, R.J and Offodile, O.F. Forecasting management philosophy life cycles: a comparative study of Six Sigma and TQM. Quality Management Journal. 2005; 12 (2), 34–46.
23. http://tech-faq.com/six-sigma.shtml. Date of retrieval: 24 April 2016.
24. Nave, D. How to Compare Six Sigma, Lean and the Theory of Constraints. A framework for choosing what's best for your organization. Quality Progress-March. American society for quality. 2002.
25. Stamatis, D.H. Six Sigma and beyond-foundation of excellent performance. 2002.
26. http://www.pharmamanufacturing.com/articles/2004/155.html. Date of retrieval: 27 April 2016.
27. Ruth II G. Capability index mystery solved. Six Sigma Forum Magazine May 2005, 17–21.
28. Mohammed Raihan Chowdhury. Process capability analysis in pharmaceutical production. International Journal of Pharmaceutical & Life Sciences, Mar 2013, 2(2), 85.
29. http://www.epa.gov/greenchemistry.html. Date of retrieval: 01 May 2016.
30. Victoria. F. Samanidou. Pharmaceutical analysis from a green perspective. Austin J Anal Pharm Chem. 2014; 1(4): 1016.
31. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070305.pdf. Date of retrieval: 03 May 2016.
32. Eugenie Khlebnikova. Statistical tools for process qualification. Journal of validation technology. 2012, 60-62.
33. Wargo D.J. and Drennen J.K. Near-infrared spectroscopic characterization of pharmaceutical powder blends**.** J Pharm Biomed Anal. 1996; 14: 1415–1423.
34. Sekulic S.S, Ward H.W, Brannegan D.R, Stanley E.D, Evans C.L et al. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy**.** Anal Chem. 1996; 68: 509–513.
35. El-Hagrasy A.S, Morris H.R, D'Amico F, Lodder R.A, and Drennen J.K. Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity**.** J Pharm Sci. 2001; 90:1298–1307.
36. Arwa S. El-Hagrasy, James K. Drennen. A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending. Part III: Quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics**.** J Pharm Sci. 2006; 95(2):422–434.
37. Kirsch J.D, Drennen J.K. Determination of film-coated tablet parameters by near-infrared spectroscopy**.** J Pharm Biomed Anal. 1995; 13: 1273–1281.
38. Kirsch J.D, Drennen J.K. Near-infrared spectroscopic monitoring of the film coating process. Pharm Res. 1996; 13: 234–237.
39. Reich G, Frickel H. Use of transmission spectroscopy to determine physical and functional film coat properties on tablets**.** Proc Int Symp Control Release Bioact Mater. 1999; 26: 905–906.
40. Simin Hassannejad Tabasi, Raafat Fahmy, Dennis Bensley, Charles O'Brien and Stephen W.Hoag. Quality by Design, Part II: Application of NIR Spectroscopy to monitor the coating process for a Pharmaceutical Sustained Release product. J Pharm Sci. 2008; 97(9): 4052–4066.
41. FDA, Guidance for Industry—Q8 (R2) Pharmaceutical Development. Rockville, MD, Nov 2009.
42. https://books.google.co.in/books.html. "Pharmaceutical Manufacturing Handbook: Regulations and Quality. Date of retrieval: 05 May 2016.
43. P. Bhandola. Leveraging Change for Continuous Process Improvement. Pharmaceutical Technology. 2015; 39(10): 62-68.
44. FDA, Guidance for Industry – Request for Quality Metrics. Rockville, MD, July 2015.
45. EMA, "Guideline on process validation for finished products - Information and data to be provided in regulatory submissions". London, UK, Nov 2014.
46. Guideline on Process Validation, EMA/CHMP/CVMP/QWP/70278/2012-Rev1, Draft, 29 March 2012, pp.no.6.
47. ASTM E2537-08: Standard Guide for the Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing. Annual book of standards, Vol 14.05, ASTM international, west Conshohocken, PA, 2008.
48. Falce L, Morreale A, Girani C. Process Validation of Legacy Product. Pharmaceutical Technology Europe. 2015, 27(4).
49. Loyd V. Allen. The Gap Analysis for non-sterile compounding. Secundum Artem.2015; 17(2),1.
50. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf. Date of retrieval: 08 May 2016.
51. Woollen, Stan W. "Data Quality and the Origin of ALCOA" The Compass – summer 2010.
52. Christopher H.W, Lizzandra R.G, "The Data Quality Equation – A Pragmatic Approach to Data Integrity | IVT, August 2015.
53. MHRA, GMP Data Integrity Definitions and Guidance for Industry, Rev1.1, March 2015.
54. FDA, Draft Guidance for Industry – Data Integrity and compliance with CGMP". Rockville, MD, April 2016.
55. http://www.kneat.com/technology/computer-system-validation.html. Date of retrieval: 11 May 2016.

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