INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

RECENT TRENDS IN VALIDATION

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ABSTRACT

This article outlines the general principles and approaches that are appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), collectively referred to in this article as drugs or products. This article incorporates principles and approaches that all manufacturers can use to validate manufacturing processes and cleaning processes. This article aligns process validation activities with a product lifecycle concept and encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

WHAT IS THE CHANGE IN TREND?

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, and equipment sanitation and purified water production. The concept of validation was first developed for equipment and processes and derived from the engineering practices used in delivery of large pieces of equipment that would be manufactured, tested, delivered and accepted according to a contract

Simply stated, validation means that the pharmaceutical companies must document each step of the manufacturing process, including packaging, and verify irrefutably that each step, each process, each machine does exactly what it's supposed to do each time.

But as the times changed, the concept of validation has taken new routes. The definition of validation as on today is 'The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.'

In the past, process validation emphasis has been on collecting large quantities of data from validation batches, leading to a perception of process validation as largely a documentation exercise. Present approach requires the manufacturer to collect data throughout the product life cycle and

evaluate it for evidence that it supports a quality process.

In the past, equipment simply controlled its own functions; three or four other systems tracked what was being fed to it, or measured downtime, or tracked performance. But now the machine "knows" when it's a good machine and when it's not. This requires a lot more validation, but in the end it makes the process easier and more efficient, especially when it comes to changeovers, which are another huge challenge to validation.

The industry responded to the cGMP report with Process Analytical Technology, or PAT, a system to design, analyze, and control manufacturing and packaging processes through timely measurements of critical quality and performance attributes. The goal of PAT is to understand and control the processes with the assumption that quality can't be tested into products, but rather should be built in by design.

FOCUS ON ALIGNMENT WITH 'PRODUCT LIFE CYCLE'

A three stage approach has been given to Process validation:

1. Process Design
2. Process Qualification
3. Continued Process Verification

The focus has been shifted from validation of individual parts of a process to a more collective 'Process Validation' effort that takes a more holistic view of the process, highlights the GxP critical parts of the process and focuses efforts and resources on the most critical aspects.

Each of the above mentioned stage is briefly summarized below:

Stage	Intent	Typical Activities
Process Design	• To define the commercial process on knowledge gained through development and scale up activities • The outcome is the design of a process suitable for routine manufacture that will consistently deliver product that meets its critical quality attributes	• A combination of process and product design (Quality by design) • Product development activities • Experiments to determine process parameters, variability and necessary controls • Risk assessments • Other activities required to define the commercial process • Design of experiment testing
Process Qualification	• To confirm the process design as capable of reproducible process manufacturing	• Facility Design • Equipment and utilities qualification • Process performance qualification • Strong emphasis on the use of statistical analysis of the process data to understand process consistency and performance
Continued Process Verification	• To provide ongoing assurance that the process remains in a state of control during routine production through quality procedures and continuous improvement initiatives	• Proceduralised data collection from every batch • Data trending and statistical analysis • Product review • Equipment and facility maintenance • Calibration • Management review and production staff feedback • Improvement initiatives through process experience

- Here we shift the focus from completing a suite of documents, to ensuring that equipment and utility qualification activities are appropriate and complete.
- Here equipment qualification in practical terms refers to IQ, OQ and equipment PQ as well as process qualification refers to prospective process validation batches.

PROCESS DESIGN

- Takes into account sound scientific methods, principles and good documentation practices and follows comprehensive approach as laid down in ICH Q10.
- Decisions and justification of controls are documented and reviewed.
- Provides key inputs such as intended dosage form, quality attributes and a general manufacturing pathway and even takes into account variability posed by different component lots, sites, operators, environment and measurement systems
- Laboratory or pilot scale model are considered representatives of commercial process
- Risk analysis tools to screen potential variables during design of experiment.

PROCESS QUALIFICATION

Facility qualification is required to ensure that the buildings and facilities are in line with regulations and the products to be made. Qualification of utilities and equipment which is essential for those which have direct product contact as well as Qualification to identify studies and tests, criteria to assess outcome, timing, responsibilities and procedures

Process Performance Qualification

It combines actual facility, utilities, qualified equipment, trained personnel with the commercial process, control procedures and components to produce commercial batches. PPQ is essential before commercial distribution and is based on overall product and process understanding and demonstrable control and for this accumulated data from experiments, laboratories, pilot and commercial batches to be used. PPQ may involve higher level of sampling, additional testing and greater scrutiny of process performance. The duration for higher level of sampling is dictated by volume of production, process complexity and understanding and experience with similar process or products. PAT is helpful in measuring in real time, thus helping in adjusting the process

Process Performance Qualification Protocol

- Manufacturing conditions, Operating parameters, Processing limits and component inputs
- Data – collection and when and how of evaluation
- In-process, release and characterization tests with acceptance criteria
- Comprehensive sampling plans
- Statistical methods for analyzing collected data e.g. intra-batch and inter-batch variability
- Deviation and non-conformance
- Documentation and analysis
- Design of facilities, qualification of utilities and equipment, personnel training and qualification and verification of material sources
- Validation of analytical methods at all stages
- Review and approval of protocols

Process Performance Qualification Protocol – Execution and Report

- Any departure must be made according to written procedures and departure to be justified and approved and discuss and cross-reference all aspects of the protocol and thus summarize and analyze data as per protocol.
- Evaluate any unexpected observations or additional data collected and even discuss all non-conformances and aberrant test results.
- Recommend corrective action or changes to be made to existing procedures and controls and conclude whether the process meets the conditions as per protocol or otherwise, it should recommend further action before compliance can take place

CONTINUED PROCESS VERIFICATIONS

It includes developing a system for detecting unplanned departure and thus adherence to cGMP. Continued process verification recommends correction and evaluation of accumulated data. Ongoing programmes are organized to analyze product and process data relating to product quality including statistical trending and review. It also evaluates process stability and capability and even monitors sources of variation not previously detected as Alert and action limit are parameters are variable. It emphasizes continuous monitoring of sampling process parameters and quality attributes and even in establishing basis for level and frequency of routine sampling and monitoring. Assessment of defects, complaints, OOS, process deviation, yield variation, adverse events, batch record and incoming material records is also a part of continued process verification as data gathered at this stage leads to improvement and/or optimization of process and plan changes depending on analysis of data. It proposes to analyze the impact of change on product quality, additional process design and qualification activities.

THE GOLDEN THREE BATCHE

Manufacture of three batches for process validation has become industry standard. It is the responsibility of the manufacturer to provide assurance that the process is adequately qualified with the use of statistical methods to provide objective evidence. In practice this may mean that three batches are sufficient to provide necessary data, or it may be that more are required. The manufacturer needs to justify, assess and clearly state those requirements during the preparation of PQ protocol.

Revision of Worst Case Concept

The concept till now is this "A set of conditions encompassing upper and lower limits and circumstances, including those within the SOP's which pose the greatest chance of process and product failure when compared to ideal conditions." Attempting to cover worst case conditions in process validation would often mean that parameters applied to validation batches bore little resemblance to the standard conditions. Present day concept is "The commercial manufacturing process and routine procedures followed. PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process." This shifts the responsibility for processing variability to the process design stage of validation activities. It is intended that product development studies and risk analysis should address process variability and quantify the effects on the product where possible.

Revision of Re-validation Concept

Till date, re-validation of processes is done when changes to a process are introduced or when process variation is detected. The present concept involves ongoing assessment of process data against variability limits established during the first two stages of process validation. The sorts of changes which previously required re validation may now be adequately addressed through a company's continued process verification procedure incorporating the use of statistical and qualitative methods, as well as risk assessment. The use of these methods may also provide impetus to re perform all or parts of stage 2 of validation.

The Consistency of Standards

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change. Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the

process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented. In summary, the manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

Documentation

Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification. CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record and supporting procedures) are key outputs of Stage 1, process design. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability.

Cleaning Validation

It is necessary to validate cleaning procedures for the following reasons:

1. It is a prime customer requirement since it ensures the purity and safety of the product.
2. It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.
3. It also assures the quality of the process through an internal control and compliance.

Cleaning Procedures

- Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment.
- Following parameters are to be considered during cleaning procedures.
  - A. Equipment Parameters to be evaluated
    - A.i. Identification of the equipment to be cleaned
    - A.ii.'Difficult to clean' areas
    - A.iii. Property of materials
    - A.iv. Ease of disassembly
    - A.v. Mobility
  - B. Residues to be cleaned
    - B.i. Cleaning limits
    - B.ii.Solubility of the residues
    - B.iii. Length of campaigns
  - C. Cleaning agent parameters to be evaluated
    - C.i. Preferable materials that are normally used in the process
    - C.ii.Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required)
    - C.iii. Solubility properties
    - C.iv. Environmental considerations
    - C.v. Health and safety considerations
  - D. Cleaning techniques to be evaluated
    - D.i. Manual cleaning
    - D.ii.CIP (Clean-in-place)
    - D.iii. COP (Clean-out-of-place)
    - D.iv. Semi automatic procedures
      - D.v. Automatic procedures
      - D.vi. Time considerations
      - D.vii. Number of cleaning cycles

TESTING METHODS

The basic requirements of the analytical methods should have the following criteria.

1. Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.
2. Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.
3. The testing analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside the allowed range.

Specific and non-specific methods

- A specific method detects unique compounds in the presence of potential contaminants. Ex: HPLC.
- Non-specific methods are those methods that detect any compound that produces a certain response. Ex: Total Organic Carbon (TOC), pH and conductivity.

High performance liquid chromatography

Almost every pharmaceutical company has an HPLC instrument, utilizing a variety of detectors. These include UV, fluorescence, electrochemical, refractive index, conductivity, Evaporate light scattering detector (ELSD) and many others. The vast majority of techniques described in the literature are for the determination of surfactants in concentrated products. Therefore, the limits of quantitation and the limit of detection are rather high. Analysis of anionic and cationic surfactants is done by HPLC and Capillary electrophoresis (CE), where as amphoteric surfactants are analysed by HPLC, CD and ELSD.

Capillary electrophoresis

Capillary electrophoresis can be used for many different types of analysis, viz; separation, detection and determination of sodium lauryl sulphate in cationic, anionic and non-ionic surfactants. Another technique known as Micellar electro kinetic capillary chromatography is used for the separation of non-ionic alkyl phenol polyoxy ethylene type surfactants.

Total organic carbon (TOC)

Presently total organic carbon is used widely in the pharmaceutical industries for various purposes. TOC is determined by the oxidation of an organic compound into carbondioxide. The oxidation can occur through a number of mechanisms depending on the instrument being used. TOC is used for the analysis of detergents, endotoxins, biological media and poly ethylene glycol.

Ion chromatography

Ion chromatography can be used for the analysis of inorganic, organic and surfactants present in the cleaners. Most cleaners contain sodium and/or potassium. The ion chromatography detection technique of suppressed conductivity is more sensitive to potassium ions than to sodium ions. Very low levels of cleaning agents can be detected by using this technique.

Others

1. Thin layer chromatography (TLC): TLC is widely used for the qualitative determination of surfactants.
2. Atomic absorption spectroscopy (AAS): AAS is used for the determination of inorganic contaminants.
3. Bioluminescence: It is useful for biologicals. This type of analysis usually uses ATP-bioluminescence.
4. Optically simulated electron emission (OSEE): In some cases the limits of residue are very less that they can't be detected by conventional methods. OSEE is a very sensitive method that can be used for both qualitative and quantitative manner in this regard.
5. Portable mass spectrometer: Portable mass spectrometer can be used to detect ultra sensitivemeasurements and identification of the residue.
6. Additional techniques: These include Enzyme-Linked Immuno Sorbent

Assay (ELISA) and Limulus amaebocyte lysate (LAL) technique.

METHOD VALIDATION

It is very important to scientifically establish the residue limit prior to choosing the method of analysis. This includes the limit in the analytical sample and the limit in the next product. This will ensure the ability of the chosen method to detect and quantitate the limit present. Once the technique for analysis has been chosen, it is very important to validate the method used.

Validation report

A validation report is necessary to present the results and conclusions and secure approval of the study. The report should include the following information:

1. References to all the procedures followed to clean the samples and tests.
2. Physical and analytical test results or references for the same, as well as any pertinent observations.
3. Conclusions regarding the acceptability of the results, and the status of the procedures being validated.
4. Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
5. Review of any deviations from the protocol.
6. When it is unlikely that further batches of the product will be manufactured for a period of time, it is advisable to generate reports on a batch by batch basis until such time. The report should conclude an appropriate level of verification subsequent to validation.

An effective cleaning validation maintenance programme

When a minimum of three cleaning validation runs get completed and if the results meet the acceptance criteria, then the cleaning procedures would be demonstrated sufficiently and consistently to remove chemical and detergent residues from equipment surfaces during the study in order to meet the pre-established criteria. However, overtime and certain other factors can decrease the efficiency and consistency of the cleaning program. They are:

1. Operator variability
2. Equipment aging and repair
3. Potential non representative results and monitoring programmes
4. Changes to the product, equipment and process.

Operator variability

Additional questions to be asked when evaluating the cleaning process:

1. Does the equipment have to be scrubbed by hand?
2. What is accomplished by hand scrubbing as opposed to just a solvent wash?
3. How variable are manual cleaning processes from batch to batch and product to product?

These questions are all related to manual cleaning. The last question focuses on sources of variation associated with a manual cleaning process that is operator variability. Many companies rely on intensive training programmes to reduce operator variability.

Equipment aging and repair

Through normal use, the smoothness and structural integrity of the equipment surfaces can change over time. As the surface becomes rougher, it is more difficult to clean because it has a greater contact area that can adsorb and could trap more chemical residues. Repairing a piece of equipment or installing new parts could create new stress centers, leading to difficulty in cleaning the surfaces.

To make an equipment maintenance programme, the following points could be considered

1. Enforcement of standard operating procedures (SOPs).
2. A routine functionality check.
3. Mechanical maintenance.
4. A cleanability evaluation programme for equipment repair.

Potential non-respective results and monitoring programme

However, cleaning validation resulting from three runs does not provide a high degree of confidence, especially for manual cleaning procedures. Operators may introduce a bias in their cleaning during cleaning validation process. To confirm the validity of extrapolating validation results to future operations, a monitoring programme can be implemented to ensure a consistent cleaning capability after the cleaning validation has been completed.

Monitoring programme can be done in either of the following two ways.

1. Difficulty in cleaning the equipment
2. Difficulty in cleaning the product and equipment.

The monitoring programme provides a mechanism to verify the capability of the cleaning procedures, the efficiency of the training programme and the effectiveness of the equipment maintenance programme.

Changes to the products, equipment & process

When new products and equipments are added to the cleaning validation programme, revalidation of the acceptance limits for all of the products and equipments involved in the original cleaning validation study may be necessary. The acceptance limits for a cleaning validation programme usually take into account parameters viz. the product, equipment matrix, potency, daily dose and batch size.

CONCLUSION

- In all stages of the product life cycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient.
- An integrated team approach to process validation that includes expertise from a variety of disciplines (e.g., process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance) is recommended.
- Project plans, along with the full support of senior management, are essential elements for success.
- All studies should be planned and conducted according to sound scientific principles, appropriately documented, and approved in accordance with the established procedure appropriate for the stage of the life cycle.
- Where as a cleaning validation programme should contain the assessment of equipment and products, assessment of the impact of a process on routine process, determination of an appropriate cleaning agent and method, determination of acceptance criteria for the residues, determination of a degree of evaluation required to validate the procedure, decisive on the residues to be tested based on solubility and toxicity, development of sampling and analytical methods for recovery and detection of residues.

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