ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (9) 2013, 65-73

REVIEW ARTICLE

OVERVIEW OF PROCESS VALIDATION FOR LYOPHILLIZED PRODUCTS

Prajit Kumar Acharya[1], Saurabh Seth[2], Meenakshi Shadangi[2]

[1]Granules India Ltd. Hyderabad, Andhra Pradesh, India

[2]Akums Drugs & Pharmaceutical Ltd. Haridwar, Uttarakhand, India.

Received 10 September 2013; Revised 15 September 2013; Accepted 18 September 2013

ABSTRACT

In the era of freeze drying, the process validation plays an essential role. In January 2011, the U.S. Food and Drug Administration published new process validation guidance for pharmaceutical processes. The new guidance debunks the long-held industry notion that three consecutive validation batches or runs are all that are required to demonstrate that a process is operating in a validated state. Instead, the new guidance now emphasizes that the level of monitoring and testing performed during process performance qualification (PPQ) studies must be sufficient to demonstrate statistical confidence both within and between batches. The discussion in this article discusses an analysis of the critical process parameters and their respective impact on the development of lyophilized parenterals.

INTRODUCTION:

Drugs are critical elements in health care. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical, physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labelling and validation. They must be manufactured to the highest quality levels.

Lyophilization (freeze-drying) is often used to prepare dry pharmaceutical formulations to achieve commercially viable shelf lives. The process comprises three steps: freezing, primary drying, and secondary drying. As water freezes in the first step, the dissolved components in the formulation remain in the residual liquid, a phase termed the *freeze-concentrate*. At the point of maximal ice formation, the freeze concentrate solidifies between the ice crystals that make up the lattice. Under appropriate lyophilisation conditions, the ice is removed by sublimation during primary drying, leaving the remaining freeze-concentrate in the same physical and chemical structure as when the ice was present. Residual water in the freeze-concentrate is removed in the secondary drying step. The conditions under which pharmaceutical products are freeze dried are subject to stringent standards. Satisfying these requirements is essential for companies wishing to prove that their products have been safely produced and are suitable for sale both at home and overseas. The high financial value of pharmaceutical products makes it essential that correct procedures are followed. For this reason, it is critical that the various stages in the freeze drying process are precisely controlled and independently monitored in accordance with GAMP guidelines.

Process validation in pharmaceutical industries is a continuing and evolving process which indicates regulation of all aspects of the process. The tradition of controlling the process arose long before the theory or analytical methods underlying it were developed. Validation of processes was premeditated using empirical methods that were based on sixth sense ("feel") and far-reaching process experience. Most of the reasoning involved was nonmathematical and this approach would be termed as unscientific trial and error. 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. Validation, as it is known today, has developed from the need to maintain quality, consistency, and above all, safety and efficacy. Pharmaceutical process validation can be defined as any operation that make conform some internal physical characteristic that is important for ensuring safety and efficacy. Pharmaceutical Process Validation is one of the most indispensable parts of Quality System Regulations. Quality System Regulation of Code of Federal Regulations Title: 21, Volume 8, Revised as of April 01, 2013 states

*Corresponding author: Prajit Kumar Acharya / Email: pkacharya10@gmail.com

that each and every manufacturer must establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met. Process Validation is an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances. Process validation make systematic assessment of the design an integral part of development. As a result, deficiencies in processes, and discrepancies between the proposed processes and requirements, are made evident and corrected earlier in the development process. Process controls increase the likelihood that the process transferred to production will translate into a finished product that is appropriate for its intended use.

Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.

FDA's Perspective on Process Validation:

The basic principle of process validation is that a drug should be produced that is fit for its intended use. *USFDA's Guidance for Industry on "Process Validation: General Principles and Practices"* states that *Process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. This indicates that the number of process validation batches or runs required to demonstrate that a pharmaceutical process is operating in a validated state should be based on sound statistical principles. The old rule of "three consecutive batches and you're done" is no longer sufficient. Instead, the new guidance now emphasizes that the level of monitoring and testing performed during process performance qualification (PPQ) studies must be sufficient to demonstrate statistical confidence both within and between batches. In some cases, three qualification runs may not be enough. It also emphasizes process validation involves a series of activities taking place over the lifecycle of the product and process. The new definition of process validation is a significant paradigm shift from the original concept, embracing the basic principles of scientific understanding put forth in ICH Q8 AND ICH Q9 as a foundation for controlling process variability.

TYPES OF PROCESS VALIDATION:

Prospective Validation: This approach to validation is normally undertaken whenever the process for new formula must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production. During the product development phase the production process should be broken down into several steps. Each process should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product.

Retrospective Validation: Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment.

This approach is rarely been used today because it's very unlikely that any existing product hasn't been subjected to the Prospective validation process. It is used only for the audit of a validated process. Some of the essential elements for retrospective validation are:

1. Batches manufactured for a defined period (minimum of 10 last consecutive batches)
2. Number of lots released per year
3. Batch Size / Strength / Manufacturer / Year / Period
4. Master manufacturing / packaging documents
5. Current specifications for active materials / finished products.
6. List of process deviations, corrective actions and changes to manufacturing documents.
7. Data for stability testing for several batches.
8. Trend analyses including those for quality related complaint.

Concurrent Validation: It refers to repeating the original validation effort or any part of it and includes investigation review of existing performance data. It could also be termed as requalifying, revalidating or even recertification of an ongoing process in response to a significant change in product components,

manufacturing, equipments, facilities, batch size or manufacturing procedure. It may be practical under certain circumstances. Examples of these may be:

1. When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site.
2. Where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients.
3. When the number of lots evaluated under the retrospective validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control.

Revalidation: It means repeating the original validation effort or any part of it and includes investigation review of existing performance data. Some of the examples of revalidation are given below:

1. Major Change in the manufacturing process which may affect the quality of the product.
2. Changed in the batch size.
3. Change in the batch formula.
4. Change in the manufacturing location.
5. Modification / Change in equipment used which is expected to affect the quality of pharmaceutical product.
6. Change in the specification and / or change in the source of Active Pharmaceutical Ingredient.
7. Change in Primary Packaging material.

PRINCIPLES OF PROCESS VALIDATION:

The basic principle is to obtain harmony between the results obtained and requirements, which include/ supports:

1. Specified requirements and objectives.
2. Available means
3. Choices which are justified in relation to objectives
4. Each stage should begin when the previous stage is over.

The following scheme may be suggested:

1. Aim versus objective
2. Validation Protocol
3. Challenging the Critical Process Parameters
4. Process as a whole and flow diagram.
5. Protocol versus report: procedures, sampling, testing, reporting and results.
6. Evaluation and recommendations including frequency for revalidation.

PHASES OF VALIDATION: The activities related to validation studies may be classified into three phase:

Phase – 1: Pre-validation phase or the qualification phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipments qualification, installation qualification, master production documents, operational qualification, process capability.

Phase – 2: Process validation phase (process qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the worst case conditions.

Phase – 3: Validation maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications, to the production process, and that all SOP's have been followed, including change control procedures.

At this stage the validation team also assures that there have been no changes / deviations that should have resulted in requalification and revalidation.

STAGES OF PROCESS VALIDATION:

Most importantly, companies that master the concepts of technologic, design, and regulatory space can transfer that understanding to drug development and manufacturing throughout their operations, and thereby gain significant business benefits. The fewer deviations and rejected batches that result from greater operating flexibility reduces costs and ensures a reliable stream of supply to the market. A lightened regulatory burden and greater confidence in the ability to maintain in-specification operations frees resources for more productive investment. In short, the companies that win this space race will win on the bottom line and in the marketplace.The guidance also describes process validation activities in three stages.

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. Process predictability relies on understanding what is important to process predictability and product performance. Having a solid grasp of the formulation and product design rationale is essential to achieving that level of understanding. The formulation will provide an early glimpse as to what processing steps may become critical downstream and hence become sources of variation in the process. The product design rationale will define how the formulation, raw materials and processing steps are related to achieving the desired product performance.

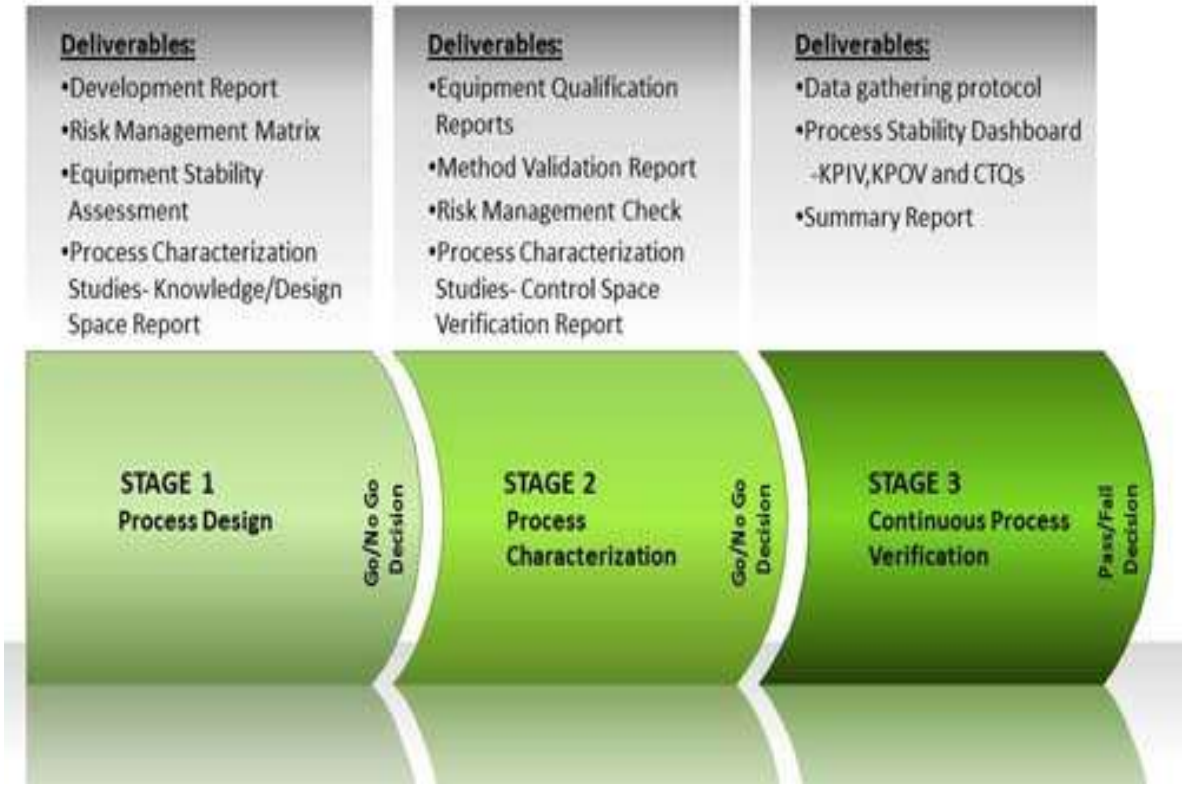

Figure 1: Schematic diagram of process design

The end of Stage 1 should provide sufficient detail to develop the **validation master plan** that will describe the approach, justification and rationale for moving to Process performance Qualification.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. As the process is developed at small scale, a process risk management tool such as a Process Failure Modes and Effects (pFMEA) can be powerful in identifying which processing steps could affect process stability at Stage 2. Before conducting any risk management it is a good idea to create a process map that captures all inputs, outputs and control variables. This can be used to discuss what CTQs will be measured and provide a risk based foundation for developing a sampling and testing strategy. Small scale and scale-up data may be captured here if a comparability argument is part of the downstream scale-up exercise to ensure there is parity between the critical output parameters as they relate to identified CTQs. The demonstration phase of the process validation lifecycle occurs in Stage 2. Before moving to this phase there are several critical precursors. First, the facility and its supporting critical utilities must be in a state of control. Secondly, the equipment must be qualified—meaning the installation qualification, operational qualification and performance qualification are all complete. Finally, the in-process and release methods used for testing must be validated, and their accuracy and precision well understood, in terms of the final control space being evaluated. These steps are essential to ensure that the unknown variability we are evaluating is attributable to the process alone.

This introduces a new term **Process Performance Qualification** (PPQ), in lieu of process validation for process demonstration. The PPQ is intended to subsume all of the known variability from the manufacturing process and demonstrate that the process predictability is sufficient to ensure the product performs as it claims to do. In this case, the big departure from past process validation approaches is that it is the cumulative understanding from Stage 1 and 2 that drives the decision that the process is predictable. The rigor applied in Stage 1 will dictate the level of characterization, sampling and testing required in Stage 2. Dedicated focus in Stage 1 will result in reduce Stage 2 cost and timeline impact.

The PPQ exercise focuses on **demonstrating process control**. Data from platform formulations and unit operations can be used to manage the risk moving forward and establish the level of characterization required in the PPQ protocol. Consequently, the old rule of "three lots and we are done" goes out the window. For simple processes with a low risk of process excursion,

e.g. high loaded dose, direct blend formulations, the PPQ may be three lots or less. For complex processes, e.g. low dose controlled release spray drying processes or mammalian cell processing, the number of demonstration lots will likely be higher. Old paradigms, supplied by FDA Guidance for such things as media fills for aseptic validation, will now require a risk-based statistical justification based upon lot size and risk tolerance. The PPQ will challenge the process control space. The **control space** represents the recommended manufacturing limits for the process. The **control limits** are typically established by moving away from the boundary limits of the design space, and selecting parameter limits in a process design space that will ensure process predictability away from the edge of failure.

There are no sacrosanct evaluation parameters for demonstrating a successful PPQ. Process Capability is a fundamental metric that can be used to compare process variability and process centering against allowable specifications. It can be used to justify AQL or LTPD sampling levels at the commercial level that could be a substantial on-going cost savings. If desired, this information will support any PAT strategy the site may have for the process downstream.

A good practice at the end of the PPQ is to go back to the risk management evaluation and demonstrate that the process risk elements identified at the outset of Stage 1 have been mitigated. This data will be the basis of managing continued improvement on the process via the change control system.

At this point, the pFMEA can be used to prioritize which key process steps and KPIVs represent areas of risk to process predictability. These areas will become the focus of characterization studies in Stage 1 and later in Stage 2.

- Equipment/Process Characterization Studies

Before beginning any characterization study, it is essential to be sure the equipment performance is stable and reproducible. Characterization studies performed on unstable equipment will introduce variability that will not be indicative of the final process. While a formal qualification process is not required, fundamental engineering characterization studies should be performed on the equipment before beginning the process studies.

When looking at the basic principles behind ICH Q8, the guidance describes a tiered exercise in which process understanding and key parameter variability is methodically narrowed as the process definition moves from the knowledge space through the design space to the control space used for manufacturing. Characterization studies need to be balanced in their experimental design. This means that early **one-factor-at-a–time** (OFAT) studies can serve as supportive data for the design of these experiments but that characterization studies should be balanced or "orthogonal" when it comes to determining the contribution to process stability from critical input parameters. While the number of lots will increase during this phase, these smaller scale studies provide the opportunity for larger sampling plans and greater process characterization than would be required with full-scale batches. Effective Stage 1 characterization studies are based on several factors:

a) Sampling Plans:

Designing a sampling plan that has the appropriate resolution to describe the process variability is important to building confidence as the process scales up and moves to validation. There is no one approach to determining the appropriate sampling plan. The FDA does not legislate a specific approach to establishing a sampling plan. Whatever approach is selected, however, must have a clearly defined rationale behind it. Possible sources and approaches for developing a sampling plan include PQRI recommendations for powder processes, ANSI Z1.4-2008, Acceptable Quality Level (AQL), Lot Tolerance Percent Defective (LTPD), or the Operating Characteristic (OC) curve. There is no right or wrong answer, but whatever sampling plan is developed must be defensible based upon the level of resolution necessary to see variation in the process.

b) Sampling Technique:

Although the equipment may not reflect the sampling challenges at full scale, demonstrating that sampling and storage methodology does not introduce variability into the process is a precursor step to performing characterization studies. A Gage Reliability and Reproducibility (GRR) study would be an effective way of demonstrating the sampling technique is robust.

c) Method Robustness:

Typically, analytical and in-process methods are validated at this stage but it is important to ensure the accuracy and precision of the method itself. Making sure the measurement tool is capable of seeing the differences in the process performance being evaluated is fundamental to knowing you are characterizing process variability and not measuring noise.

Stage 3 – Continued Process Verification: The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. The FDA is looking for a monitoring program capable of detecting gradual or

unplanned departures from the process as designed. Historically, we have used the product stability program, change control process and the Annual Product Review Process as vehicles for monitoring and assessing process stability. The challenge with this approach has always been the resolution of these systems making proactive intervention difficult to achieve when dealing with process drift. For this stage the agency is looking for a program that builds upon the process understanding acquired in Stages 1 and 2.

Stage 3 will require a monitoring program that balances sampling, testing costs and demand with process understanding. A matrix approach to sampling with a focus on looking at intra- and inter-batch variation of the KPIVs and CTQs for the process is one way to cost effectively monitor the commercial process stability. Employing Statistical Process Control, Moving Range Charts and XBar-R charts are also simple ways to evaluate if the process is wandering unacceptably. It is important to apply a data-gathering phase before establishing alerts and action limits, since the commercial process will subsume the totality of variation from the raw material, process, and testing methods. This data should drive a statistical analysis of data against the process characterization and PV lot performance. Understanding the intent behind each analysis is essential to coming to the right conclusion. Statistical software packages such as Minitab and JMP can make analysis simple and reproducible and introduce, as required, data evaluation criteria such as the Westinghouse rules which, when used to discriminate aberrant data from true process variability, can determine if further action is required. As areas of further study are identified, the risk management tools should be revisited to ensure the impact of the process variation is evaluated consistently.
Ongoing assurance is gained during routine production that the process remains in a state of control.

USFDA's guidance aligns with the process validation activities with the product lifecycle concept, along with the International Conference on Harmonization guidance for industry, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System. The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. Design Space Establishment

To identify the boundaries and variables that drive process stability it is possible to focus only on the parameters that steer the process and the corresponding Key Process Output Variables (KPOV) that affect the product CTQs. The design space will explore the boundary limits of the parameters that are critical to process stability. Identifying the KPIVs of interest can be achieved using a combination of a balanced Design of Experiments (DOE) approach and statistical analysis, such as Analysis of Variance (ANOVA) to summarize the contribution of each variable to the variation seen in the data being analyzed. A high correlation of determination (r^2) means that most of the variation seen in the data can be explained by the variables evaluated.

A major concept introduced in the Guidance is called Design Space. Briefly, this is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. In simple terms, since a fixed set of conditions does not allow the production staff to react to changing materials and conditions, ranges of settings are needed. This combination of ranges needs to be shown to give a quality product. The region of (imaginary) space bounded by these allowable variations is known as design space.
Working within the submitted Design Space is not considered as a change; thus, making a change within, for instance, hardness parameters or weight limits is certainly allowed. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post approval change process. Design Space is proposed by the applicant (producer) and is subject to regulatory assessment and approval. The Design Space is determined by experimentation.

The results of a Formal Experimental Design will, using multivariate math (e.g., partial least squares) point to the major effects on product quality and limits of "acceptable" values for them. It is defined as "a structured, organized method for determining the relationship between factors affecting a process and the output of that process." This is also known as Design of Experiments. A number of software programs are commercially available for the design of experiments; most are quite easy to use. The work comes in when the actual runs need to be done.

One key to the Design Space is known as Process Robustness. In short, this is the ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality. The more robust the process, the greater range of incoming raw material variation will still give an acceptable product. (One example might be for a solution; if the material in question is simply to be dissolved, particle size limits might be redundant. It

would be smarter to merely state "stir until dissolved" instead of specifying a set mixing time.)

Another important term introduced in Q8 is the Lifecycle of a product. This refers to all phases in the life of a product from the initial development through marketing until the product's discontinuation. It implies that we can and should control the facets of the product from development until it is no longer made by the company. This requires much more integrated discussions from the synthesis steps through production to stability testing and eventually, the decision to discontinue production.

The ability to control all the steps is the basis of Process Analytical Technology (PAT). In a nutshell, PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. Then, when being dried, it must meet certain criteria (% solvent, particle uniformity) before being allowed to proceed to lubrication, and so forth. PAT generates documentation for product improvement as well as controlling each batch to obviate failure.

Table 1: Selection of Critical Process Parameters for consideration in the validation of lyophilized parenterals:

Process /Stage	Critical Parameter
Area	Bioburden
Delumping	Screen: 1.5 mm
Purified water	Bioburden, Clarity
Water for Injection	Bioburden, BET, Clarity, Temperature of WFI
Mixing	Bubbling of Nitrogen gas, Mixing time, Impeller RPM, Total quantity of WFI
Volume make up	Quantity of WFI, Temperature of WFI:
Filtration	Screen, Pre-pressure hold test, Post-pressure hold test, Filtration Pressure
Freezing	Shelf Temperature, Chamber Temperature, Rate of Freezing, Holding Time, Distance between the shelf, Distance between the vials
Thermal Treatment	Shelf Temperature, Chamber Temperature, Holding time
Primary Drying	Shelf Temperature, Chamber Temperature, Holding time, Rate of Drying, Vapour Pressure of Condenser
Secondary Drying	Shelf Temperature, Chamber Temperature, Holding time, Rate of Drying, Vapour pressure of Condenser
Unloading	Rate of Cooling, Shelf Temperature, Holding Time, Chamber Temperature
Finished product	Test as per finished specification

Locking Down Process Parameters: Short-Sighted:

Moreover, even if this approach had resulted in the adjustment of a process parameter to yield in-spec product, the resulting improvement would likely have been short-lived. Historically, many manufacturers have taken this approach, and locked down process parameters.

The problem is that differing batches of raw materials are never entirely uniform over the long term and eventually, bad batches recur. Establishing flexible process parameters would allow for much more effective problem-solving and get to the heart of the problem once and for all. Fortunately, it is just this kind of approach that is envisioned in ICH Q8 and advanced by the FDA's Process Analytical Technologies (PAT) initiative, whose goal is to improve the control and understanding of drug manufacturing processes.

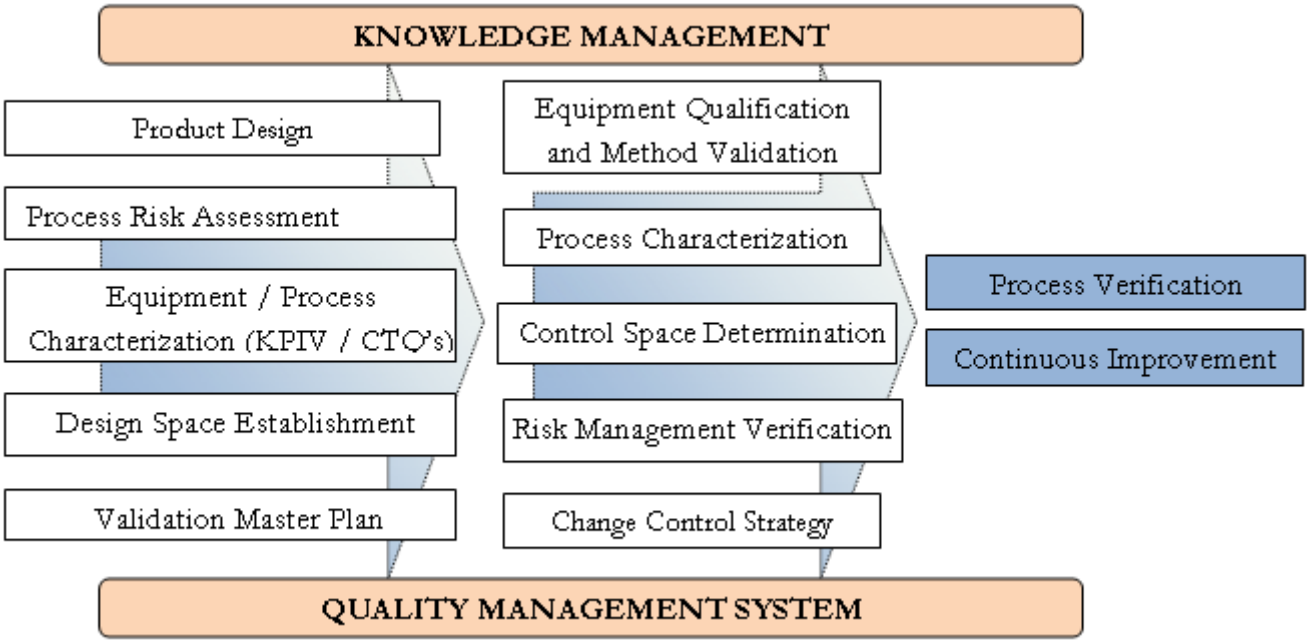

Figure 2: Interrelation between Knowledge Management and Quality Management System.

Knowledge Management:

Underlying the new guidance is the need for proactively establishing a system for knowledge management. This means ensuring all parties involved in the development, analysis and evaluation of the data and process have a solid understanding of past performance and its implications on process stability and product performance. Consolidating the information in a central document or repository will ensure some continuity of learning and will allow continuous improvement or CAPA activities to build upon best practices of the past.

Quality Management System (QMS):

The largest paradigm shift within the new guidance is the Quality function. Moving away from a product centric QMS requires that Quality be intimately involved in the evaluation and decision-making criteria as the process moves through each stage. It will require a heightened level of scrutiny to make sure all supportive elements are in place. For example, ensuring critical monitoring systems are calibrated will beg the question: "Is it single point or three point calibration?" Method capability will focus on accuracy and precision and interference points. Ensuring that controlling and measurement tools are capable will become the foundation for managing the QMS, rather than the QMS procedures and documentation audit trail. To facilitate both the knowledge management and QMS paradigm shifts, a milestone or stage gate approach to process validation is an effective way to ensure all key stakeholders and decision makers remain on board with the new process-centric philosophy.

CONCLUSION:

The new Process Validation guidance represents a dramatic shift from the 1987 FDA guidance issued to industry. While less prescriptive, it provides a sufficiently descriptive framework for industry to create a scientifically driven approach to demonstrating process predictability. There is no single answer to this guidance, and a structured roadmap, with clearly defined deliverables at each milestone will ensure that the philosophical and technical components required to demonstrate process predictability will be applied in a uniform fashion across the organization. In addition, this uniform approach to process validation will allow the organization to reap the benefits of a more focused validation effort, potentially reducing the cost of Stage 2 PPQ and resulting in products and processes which are both stable and predictable. The continued process verification stage could be considered a continuum from the end of process qualification stage until product discontinuation. For ease of representation this extended phase could be divided into an initial sub-stage (a) where sufficient data are being generated to produce variability estimates, and a subsequent sub-stage (b) of so called routine operation, where levels of sampling and monitoring may be reduced compared with earlier stages. There are two key challenges during the process that make close control particularly important.

The first, during the initial freezing stage, is the need to ensure that the product is completely frozen before the chamber is evacuated. To achieve this, a long stabilization period is needed, during which the operator may need to manually check and confirm that the process is ready to proceed to the next stage. It is also imperative to ensure that the freezing process itself is properly carried out, as the product can easily be spoiled if not frozen at the correct rate.

The second challenge is during the Secondary phase, where it is important to make sure that the water does not boil off too quickly, which could otherwise ruin the product. This requires careful control of the temperature. Given the potential for error, it is essential to have a control system that can both maintain the required conditions for freezing and heating and also respond quickly to address any potential variations in process conditions. The foundation of validation, the methodology behind validation, and the need for validation will likely remain a key aspect of the industry we work in. This review article reflects the current industry trends and serves as an educational tool in our progressive industry. The validation process extends from the very basic specifics (how each item works and interacts with another item) to a very broad theological and methodical investigation of how the system and processes perform. Its scope encompasses documentation, revision control, training, and maintenance of the system and process. Evidence of validation should be seen at the corporate level, and be reflected in the management structure. Validation is not just a set of procedures and rules to satisfy FDA, validation is a method for building and maintaining ***QUALITY***. Ideally, validation starts in the very beginning, in the laboratory. In the lab, scientists discover exactly how the product reacts, as well as the parameters that are required to produce such a product. They learn under what conditions the product fails or becomes unstable, unusable, and when its quality begins to suffer. Once the laboratory has established the boundary processing criteria, this information can then be used for establishing requirements for validation. Validation of a system never truly ends.

REFERENCES:

1. Agalloco J. Validation: an unconventional review and reinvention. PDA J. Pharm. Sci. Tech. 1995; 49: 175 – 179.
2. Aleem H, Zhao Y, Lord S, McCarthy T, Sharratt P. Pharmaceutical Process Validation: an overview. J. Proc. Mech. Eng. 2003; 217: 141 – 151.
3. Nash RA. Pharmaceutical Process Validation. 3rd edition 2003: 159 – 180.
4. Swarbrick, James. Encyclopedia of Pharmaceutical Technology. Informa Health Care. 2007 (3rd Illustrated ed.): 1170.
5. "Guidelines on General Principle of Process Validation" (US Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, USA, 2011).
6. Nash RA and Wachter AH. Pharmaceutical Process Validation; 3rd ed; Marcel Dekker publication. 2003: 432 – 434.
7. Levin M, Pharmaceutical process scale-up, Marcel Dekker, Inc. New York. 2002: 313 PMid:11897257
8. Quality Management System – Process Validation Guidance by SG3 GHTF/SG3/N99, 2nd ed; 2004. P. 10.
9. Federal Food Drug and Cosmetic Act, Title 21 U.S. Code, Section 501 (a) (2) (b).
10. Rathore S Anurag, Noferi F Joseph, Arling R Edward, Sofer Gail, Watler Peter and Leary O Rhona. Process Validation How Much to Do and When to Do it, BioPharm; 2002.
11. Chao AY, St John Fobes E, Johnson RF, Von Doehren P. Prospective Process Validation In: I Berry, RA Nash, eds Pharmaceutical Processing Validation, Marcel Dekker, NewYork, 2003.
12. FDA 483, Warning Letter to Abraxis Bioscience, Inc., 11777 San Vincete Blvd, Suite 550, Los Angeles, CA 90049; 18th Dec 2006.
13. Good Manufacturing Practices for Pharmaceutical Products, In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, 32nd Report, Geneva, WHO, (1992), p 14 – 79.