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Current Features of USFDA and EMA Process Validation Guidance

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ABSTRACT

Pharmaceutical validations are part of cGMP regulations. The validation provides justification based on sound scientific knowledge of product quality attributes for in-depth process understanding to develop process control strategy in first stage. In second stage confirmation of process control parameters influencing the quality attributes of products by designing of experiments. Further in stage to process performance qualification is done whereas in third stage continuous monitoring of process is carried out to provide the strong evidence that the process is under control during the manufacturing of products with required quality attributes. The present review describes the way how to go for validation of particular process. Also the review describes USFDA and EMA guidance on validation with modern lifecycle approach. ISPE discussion on solid tablet dosage form validation is taken as example for process validation guidance understanding in depth.

INTRODUCTION

Quality is concept applicable at everywhere from business to successful life. Everyone wanted to buy the quality product and live the quality life as per the standards determined by them for it. As concern with pharmaceutical products, these were built for to bring the quality in health of human and animal beings. Quality directly relic on health of human and animals so control on quality parameters is became necessary, so there are stringent rules and regulation for the pharmaceutical industry all over the world. This renders them as strictly regulatory controlled industries [1,5].

Regulatory bodies took the lot of efforts to maintain the quality of pharmaceutical products as per its quality specifications that are safety, efficacy, purity, identity, strength. The USFDA, EMA regulatory agencies have been taken initiative in the form of development of new concept and strategies for maintaining the quality of pharmaceutical products. Validation refers to producing the acceptable evidence and assures that the given process can be useful for its predictable use.[1]

The revised guidance on process validation promotes the use of different ICH Q8, Q9, and Q10 guideline recommendations to bring the pharmaceutical quality as central accent in pharmaceutical industry. Process validation incorporates a life cycle approach linking product and process development to continue process verification through continuous monitoring of process parameters for assure the process is in-control during its commercial manufacturing. Process qualification is intermediate stage by which evaluation of the method constraint is done. The validation guidance is based on understanding of process and product knowledge with sound scientific methods.[1, 2,3,5]

ORIGIN OF PROCESS VALIDATION

Process validation guidance was come in force from 1987 in US through USFDA notification in *Federal Register* May 2011, with elaboration of different elements of the process validation. Process validation is part of current good manufacturing practices which had its basic foundation in CFR 211.110 (a) as follows, *"There shall be written procedures for production and process*

control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.[3].

Current process validation guidance has modern approach towards validation with basic considerations of its principle and widening the scope of validation for inclusion of modern technology implementation in pharmaceutical industry, application of quality concept and tool and quality system for production of pharmaceuticals.[1,3] The objective of process control is quality should built in products by follow up the cGMP regulation [1,3,4].

In 2008, it incorporates the collection and evaluation of data i.e. applying the statistical tools for establishing the scientific evidences of specific process to deliver the quality products[5].

Whereas in 2011, validation involves the risk-based approach and lifecycle approach for products and processes and by which one can do continue process verification for assurance of manufacturing quality pharmaceutical product by the process reproducibly.

According to 1987 USFDA guideline validation is defined as ,

"*An establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics".*

According to EMA 2001 guidance[4]

"Ensuring and providing the documentary evidences that process within their specified designed parameters are capable of consistently produced finished product of the required quality".

According to 2011 USFDA process validation guidance[1]

"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 products".

According to EMA 2014 guidance,

"The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes".

According to recent validation guidance of USFDA, EMA provides a broad meaning to validation it recommends the risk management system, sound scientific method application to the process validation. Continued process verification is new approach include the guidance for routine monitoring of the process performance to build the assurance about process in control during lifecycle of process and products. According to newer approach of guidance validation is considered as continuous event.[5]

APPROACHES TO PROCESS VALIDATION

There were two types of approaches of process validation according to USFDA 1987 guidelines i.e. prospective approach and retrospective approach. The prospective approach is applicable to new process, new product approval whereas retrospective approach is based on total historical data for evaluation of process which is implemented for saleable built-up of eminence products[4,6,7].

Whereas according to 2011 USFDA process validation guidance it recommends the product or process lifecycle approach which made up of three stages i.e. process design, process qualification, continued process verification[1,5]. According to EMEA guideline on process validation it recommends the traditional approach which is based on historical data by which evaluation of process is done. [2,8,9].

Regulatory Requirements For Process Validation

Process validation is legal requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)). According to this,

"A drug. . . shall be deemed to be adulterated. . . If. . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that

such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

STAGES OF PROCESS VALIDATION

It requires sound knowledge of products quality attributes, the process knowledge by which one can produce the quality products, identification of process variables and their impact on quality attributes of product, for development of strategy to process control and monitoring[1,10,11,15,].

Stage 1: Process Design :

It can be possible with product development stage, the lab scale designing of products require different understanding process parameters and their impact on product quality. The general manufacturing pathway can be established at this stage and knowledge gain from process and product development is responsible for process and product understanding [1,15].

Process knowledge understanding :

Lab scale process design, pilot plant scale-up technique, and technology transfer to commercial production leads to require thoroughly understanding of real working of process. Quality based design, design of experiment are the tool used for design the process at different level i.e. from lab scale to commercial production of quality products with predetermined specifications. It can be completed with the aid of numerous sources as follows,

Development phase :

Determination of different variability during product development and characterization can be possible with design of experiment. Analytical capability is required condition for monitoring the parameters which are leads to variation. Process understanding through the development stage is not possible for generic manufacturer, they find out another source for gain process understanding[16].

Prior Knowledge :

Prior knowledge is associated with another similar process which can be easily understood with experience. For natural product annual product review, deviation, complaint investigation, change control information may be used for process understanding [16].

Process Understanding through Knowledge of Unit Operation :

Process understanding is possible by having the in-depth knowledge of unit operation. Trained personnel, Selection of equipments, controlling parameters of unit operations are useful for appreciative the process.

Process certainty and Modeling :

Lab scale and small scale modeling simulation are also helpful for predicting the impact of variation output on commercial production.

Effect of Scale Change :

On large-scale up the process understanding becomes broader with multi variability parameters determination and its impact on superiority.

Approach/ Strategy for Process Control :

Once scheming of the process based on its product and process development knowledge one may require to design the process parameter for evaluating the process on the basis of strategy developed for control of different process parameters which affect the product quality [1,2].

To develop the strategy of process control, one can monitor the equipment operational limits and material analysis, which leads to production of master manufacturing and control records. Process analytical technology (PAT) is modern strategy implementation for process control. [1,2,17].

Approach for process control depends on factor like

Raw material specification :

Process control is also required the raw material which qualified its specification. The variability in raw material specification leads to wrong result with great control of process. Raw material quality control has first priority in strategy of process control[6].

Experiences with process performance :

Process performance is managing the variability with adequate control on scale effect. The determination and control of variability of process which determine same kind of control parameters and its extent to influencing the quality of product which is required for commercial production.

Stage 2: Process Qualification:

It is second stage of process validation in which confirmation is done on actual efficiency and reproducibility of process during its commercial production by evaluation of process control parameters established during process design phase. The aim of this phase is to offer strong scientific justification, increase process and product understanding level, prove adequate control on production of quality products. It is main stage of process validation because the result of this stage data will be responsible for taking the decision about market release of manufactured products[6]. It consists of two rudiments as follows,[6,15,16]

Design of facility and qualifications of utilities and equipments :

The facility is required for commercial production as per the cGMP regulation. Qualification of utility and equipment means that all the actions performed for proving that utilities and equipment are suitable for their specific use. Different planning of activity is done under this involved its IQ, OQ, PQ protocols, their reports respectively.

Process performance qualification (PPQ):

It consists of use of facility, qualified utilities and equipments, trained personals, manufacturing procedure, control procedures which are ready for production of commercial production batches. PPQ involved higher sampling, testing, and scrutiny to evaluate the process performance in

typical manufacturing conditions. The evaluation of data is done with the objective measure. The statistical methods are applied for generation of meaningful inferences. The implementation of such methods provides great scientific evidence about providing adequate assurance [6,15,22]

PPQ batches are studied for providing intra and inter-batch variability. Determination of number of batches studied for PPQ is based on risk assessment. The variables responsible for high risk required more no. of batches for PPQ study whereas low-risk variables require the very few PPQ batches in revise[6]. There are unlike strategies for determining the no. of PPQ batches require for process validation, like based on rationale or experience, target process confidence and target process capability, expected coverage. Number of batches required for PPQ based on rational and experience are as follows [22].

Residual Risk level	No. of batches
Severe	Not ready for PPQ
High	10
Moderate	5
Low	3
Minimal	1-2

Stage 3: Continued/ Persistent Process Verification:

This is part of lifecycle approach applied to process validation by FDA. EMA Process validation guidelines also recommend the new approach to process validation based on lifecycle approach with continues process verification[1,2].

Development of well designed approach towards maintenance of facility, utilities, equipment is important part of stage three. [23].

Establishing Continued Process Verification Plan :

The goal of CPV plan is to assure throughout the commercial manufacturing phase of lifecycle that the process is in state of control. The plan includes the evaluation of process capability, material specificity, in-process testing, finished product testing, qualification of equipments, utility, statistical tool for acceptance of process control criteria, estimation of variability. The

statistical method applies for estimating the strength between input-output relationship. CPV plans provide the stage for process development[17,18,23].

Continued process verification plan is done for continues monitoring of process performance during manufacturing. It gives space for process improvement as well as assures that the process is well controlled and monitored during its life cycle[1].

Concurrent Release of PPQ Batch :

Concurrent release of PPQ batches is recommended under specific condition like drug of limited demand, having short life span, to alleviate the short supply. Concurrent release batches accompanied with careful monitoring of distributed batches to get easily the customer feedback for product quality. Any complaint, failure leads to improvement of process to production of quality products by taking appropriate corrective actions[1].

FEATURES OF USFDA PROCESS VALIDATION GUIDANCE 2011

1. It utilizes the basic concept of validation and uses the statistical tool for developing the scientific evidence that process is in under control.
2. It introduces continued process verification by which one can monitor the process and having space for process improvement.
3. It further ruled out the magic No. System that manufacturer followed without recommendation regulatory bodies.
4. It replaces the validation as only documented system with collection and evaluation of data by using scientific Statistical approaches.
5. Critical Quality Attributes is replaced with process variables which directly or indirectly affect on quality specification of products.
6. Guidance based on thinking that quality should be built in products.

FEATURES OF EMA PROCESS VALIDATION GUIDANCE 2014

1. Continuous process verification is included as new approach for process validation which is based on routine monitoring on process to remain in state of control.

2. The use of extensive in-line, on-line, at-line testing is recommended for evaluation of process performance.

3. Guideline covers all the critical elements consider for commercial production process inclusion as regulatory submission for pharmaceutical products.

4. Life cycle approach is adopted in newer validation guidance. Science and risk-based approach is used to assure the process is operated within specified parameters.

5. Justification for the number of batches is based on the complexity and variability of process.

6. Re-validation becomes the part of process change or continuous process improvement.

7. Hybrid approach is suggested by the EMA guidance in which both the traditional as well as enhanced validation approach are used wherever suitable in different steps of the process.

Comparison between USFDA and EMA updated process validation guidance[24]

Table No.1: Comparison between USFDA and EMA updated process validation guidance.

USFDA Guidance	EMA guidance
For marketing approval minimum no. of batches for validation are not recommended, sufficient no. of batches are required to provide assurance based on statistical and scientific justification.	Minimum three batches are recommended for process validation for market authorization of product, with justification.
CPV is part of process validation	CPV is considered as new approach to process validation
Development and execution of validation activity are assisted by USFDA.	Validation activity is recommended for dossier submission
USFDA consider all the qualifications activity as overall validation activity.	EMA consider qualification as separate guideline as annex 15.

PROCESS VALIDATION OF SOLID DOSAGE FORM WITH MODERN RISK-BASED APPROACH:

Tablet is solid dosage form which is validated by using newer risk-based approach before the market release. The design of experiments for risk assessment, determination of equipment

qualifications, products specifications, process parameters and raw material attributes, development of process control strategy in such a way that outputs obtained through the efficient and safe process design, operation, and its evaluation of process performance leads to build the strong scientific justification for production of quality product consistently and efficiently is the main objective of process validation[20,21,22].

Product knowledge determines its critical quality attribute which are given the information about the quality products. E.g. for tablet dosage form appearance, identity, assay, impurities, dissolution, content uniformity are the quality parameters which directly affect the general specification of pharmaceutical products i.e. quality, safety, efficacy[22].

Cause of risk is associated with the variables monitored in each unit operation and effects are obtained results from testing of CQA of products which directly affect the quality of the product by designing of experiment are helpful for risk evaluation prior to process development study[22].

Cause and effect matrix diagram can be prepared as follows.

Table No. 02: Cause and effect matrix diagram.

CQA/Unit operation	Dispensing	Blending	Lubrication	Compression	Coating	Packaging
Appearance	**L**	**L**	**L**	**L**	**M**	**L**
Identity	**M**	**L**	**L**	**L**	**L**	**M**
Assay	**M**	**M**	**L**	**M**	**L**	**L**
Impurities	**L**	**L**	**L**	**L**	**L**	**L**
Content uniformity	**L**	**H**	**M**	**M**	**L**	**L**
Dissolution	**L**	**L**	**H**	**H**	**L**	**L**
Microbiology	**L**	**L**	**L**	**L**	**L**	**L**

L: Low, M: Medium H: High, CQA: Critical Quality Attributes,

Dissolution and content uniformity are having highest risk associated with three different unit operations. Now after the application of process control strategy now all the associated risk

becomes low. This is requirement for submission to regulatory agencies to give justification for removal of associated risk from the process performance during manufacturing of quality product. Cause and effect matrix diagram of the application of process control strategy and after process development studies are as below. [23]

Table No. 03: Cause and effect matrix diagram of the application of process control strategy and after process development

CQA/Unit operation	Dispensing	Blending	Lubrication	Compression	Coating	Packaging
Appearance	**C**	**C**	**C**	**C**	**C**	**C**
Identity	**C**	**C**	**C**	**C**	**C**	**C**
Assay	**C**	**C+E**	**C**	**C+E**	**C**	**C**
Impurities	**C**	**C**	**C**	**C**	**C**	**C**
Content uniformity	**C**	**C+E**	**C+E**	**C+E**	**C**	**C**
Dissolution	**C**	**C**	**C+E**	**C+E**	**C**	**C**
Microbiology	**C**	**C**	**C**	**C**	**C**	**C**

C: Conventional Control Strategy including cGMP, C+E: Conventional Control Strategy including cGMP and elements of Enhance QBD Approach.

Continuous monitoring of process performance during routine manufacturing operation becomes the basis of stage 3 process validation strategy i.e. continued process verification which gives lifecycle approach to process validation program. It provides the room for process improvement, requalification strategy of equipments used in operations, any change control system required for process performance, and residual risk assessment evaluation during routine manufacturing conditions [23].

CONCLUSION

Pharmaceutical process validation is now becoming mandatory requirement of ANDA submission from 2013 and new drug approval for various regulatory agencies as it is important

parameter of cGMP Practices. It ensures that the process is capable of producing pharmaceutical products with quality attributes reproductively and consistently.

The earlier thinking was that process validation was useful for generating documented evidence for assurance of the process that it manufactures the products with predetermined specifications. Now the FDA changes in thinking about validation give rise to scientific evidences based on sound knowledge about products specifications and process variables evaluation.

EMA guidance also suggests the enhanced approach for process validation which is based on ICH Q8, Q9, Q10, requirements. Furthermore, it also adopts the lifecycle approach to validation from process design to commercial production of quality products consistently and efficiently. Hybrid approach, Design space verification are some important features of process validation guidance. In-line, at-line and on-line material testing are recommended by EMA guideline.

Continuous monitoring on process variables gives the risk management advantage. Furthermore, it leads to best control on process which renders for production of quality pharmaceutical products. CPV provides space for process improvement. The process validation provides all the justifications based on scientific knowledge with process design, process qualifications, continued process verification stages and using appropriate statistical tools methodology wherever required for evaluation of data during different stages of process validation to assure the given process perform efficiently and consistently and produce quality pharmaceutical products within its life span.

REFERENCES

1. Bryder M., Etling H. et al., Stage 2: Process validation; Determining and justifying Guidance for Industry, Process Validation: General Principles and Practices, Current Good Manufacturing Practices (cGMP) Revision 1, USFDA, **Jan-2011**.
2. Guideline on process validation for finished products information and data to be provided in regulatory submissions, European Medical Agency, **Feb-2014**.
3. Loftus, B. T., Nash, R. A., ed. *Pharmaceutical Process Validation*. vol. 57. New York: Marcel Dekker (1993).
4. FDA/ICH, (CDER and CBER), Q9 Quality Risk Management, guidance for industry, June 2006.
5. FDA/ICH (CDER and CBER) Q10 Pharmaceutical Quality System, guidance for industry, April 2009.
6. U.S. Food and Drug Administration. Compliance Program no.7356.002.
7. U.S. Food and Drug Administration. Guideline on General Principles of Process Validation. Rockville, MD: FDA, 1987.
8. Federal Food Drug and Cosmetic Act, Title 21 U.S. Code, Section 501 (a)(2)(B).
9. Code of Federal Regulations, Title 21, Parts 210 & 211. *Fed Reg 43*, 1978.

10. Guideline on General Principles of Process Validation, CBER/ CDRH/ CDER, USFDA, May 1987, reprinted **Feb-1993.**
11. Note for Guidance on Process Validation, CPMP/CVMP, European Agency for Evaluation of Medicinal Products, London, **March-2001.**
12. Guideline on General Principles of Process Validation, CBER/ CDRH/ CDER, USFDA, May 1987, reprinted **Feb-1993.**
13. Guidance for Industry: Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), Centre for Veterinary Medicine (CVM), January 2011.
14. Kathiresan K*, Moorthi C, Prathyusha Y, Gade B. R, Reddy B.K, Manavalan R,S ; An overview of pharmaceutical validtion: Research Journal of Pharmaceutical, Biological and Chemical Sciences, ISSN:0975-8585;October-December 2010 ; RJPBCS 1(4); Page No.1026.
15. Berry IR , Nash RA. Pharmaceutical Process Validation, 1993.
16. Castilla B, Sena FJ. Validation Documentation a Winning Approach, www.Ivthome, 2007.
17. Guidelines for Process Validation of Pharmaceutical Dosage Form – Saudi Food & Drug Authority; Version 2; February, 1992.
18. Oechslein C, Lazar M. S – Process Validation from view report of the FDA, Maas & Peither AG –GMP Publishing, LOGFILE No. 3/ February 2012.
19. Anji Reddy Padigapati, Saurabhsharma Pharmaceutical Process Validation: An Overview. *Global Journal of Pharmaceutical Research*, 2012; 1(4):766-784
20. 21 Code of Federal Regulations Parts 210 and 211, cGMP Regulations, http://www.fda.gov/cder/dmpq/cgmpregs.html.,the numbers of PPQ batches, ISPE Discussion Paper.
21. Dafni B., Butterell P. et al., Stage 3: Process Validation; Applying continued Process Verification Expectation to New and Existing Products, ISPE Discussion Paper.
22. Gipsa Pa dickakunnel, Vishal gupta, Modern FDA Guidance and Comparative Overview of FDA and EMA on Process Validation, Intern. J. of Pharm. Pharm. Sci., *Vol 6 (4),***2014**, 14-17.
23. .FDA/ICH, (CDER and CBER), Q9 Quality Risk Management, guidance for industry, June 2006.
FDA/ICH (CDER and CBER) Q10 Pharmaceutical Quality System, guidance for industry, April 2009.